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I, LEANNE MYNOTT, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 3568 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. filed on 21 October 1999.

WITNESS my hand this
Sixth day of December 1999

LEANNE MYNOTT
TEAM LEADER EXAMINATION
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COMMONWEALTH OF AUSTRALIA
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Fujisawa Pharmaceutical Co., Ltd.

AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Piperazine Derivatives"

The invention is described in the following statement:

DESCRIPTION

PIPERAZINE DERIVATIVES

TECHNICAL FIELD

The present invention relates to new piperazine derivatives and a salt thereof.

More particularly, it relates to new piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like.

Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

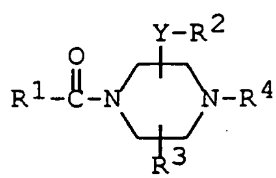
Still further object of the present invention is to provide a use of said piperazine derivatives or a pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, couph, expectoration, and the like; ophthalmic diseases such

as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

Some piperazine derivatives having pharmaceutical activities such as Tachykinin antagonism have been known as described in EP 0655442 A1 and WO 97/22597 A1.

DISCLOSURE OF INVENTION

The object compound of the present invention can be represented by the following general formula (I):



(I)

wherein

Y is bond or lower alkylene,

R^1 is aryl which may be substituted with suitable substituent(s),

R^2 is aryl or indolyl, each of which may be substituted with suitable substituent(s),

R^3 is hydrogen or lower alkyl,

R^4 is (3-pyridyl)methyl;
(3-pyridyl)ethyl;
3-(3-pyridyl)propyl;
3-(3-pyridyl)propenyl;
3-(3-pyridyl)propynyl;
pyrazolylmethyl which may be substituted with hydroxy(lower)alkyl;
pyrazolyl(lower)alkyl which is substituted with lower

alkyl, (lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl or (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)-alkyl;

piperidylmethyl;

piperidyl(lower)alkyl which is substituted with lower alkyl or (lower)alkoxy(lower)alkyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkyl;

(3-methoxymethylmorpholino)(lower)alkyl;

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl;

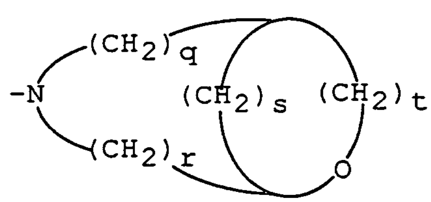
(3,5-dimethoxymethylmorpholino)(lower)alkyl;

(2,3-dimethoxymethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkenyl;

(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)alkyl;

or lower alkyl which is substituted with a saturated heterocyclic group of the formula:



(wherein

r, s and t are each integer of 1 to 2, and

q is integer of 0 to 2)

which may be substituted with one or two lower alkyl.

It is to be noted that the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom(s) and double bond, and all of such isomers and a mixture thereof are included within the scope of the present invention.

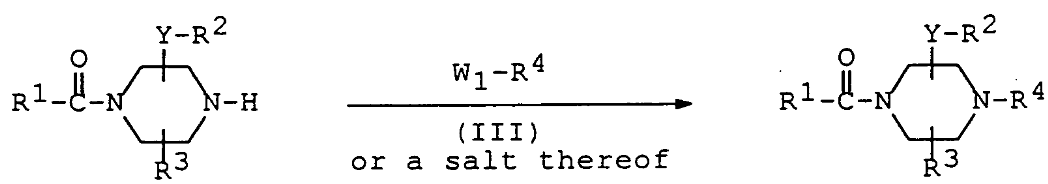
It is further to be noted that isomerization or rearrangement of the object compound (I) may occur due to the

effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

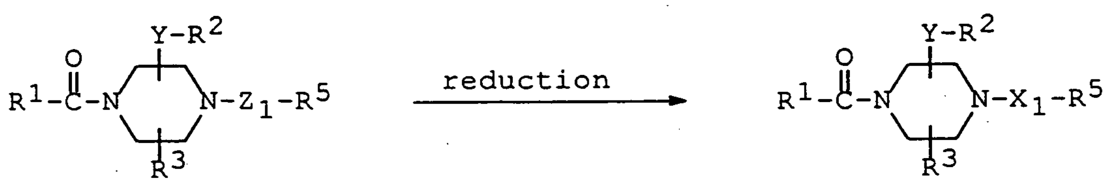
Process 1



(II)
or its reactive derivative
at the imino group
or a salt thereof

(I)
or a salt thereof

Process 2



(Ia)
or a salt thereof

(Ib)
or a salt thereof

wherein

Y, R^1, R^2, R^3 and R^4 are each as defined above,

X_1 is lower alkylene,

Z_1 is lower alkynylene,

R^5 is 3-pyridyl, and

W_1 is a leaving group.

As to the starting compounds (II) and (III), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or similar manners thereto.

Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, methylmethylene, methyltrimethylene, hexamethylene, and the

like, in which the preferred one is methylene, ethylene, trimethylene or methylmethylene.

Suitable "lower alkynylene" may include one having 2 to 6 carbon atoms, such as ethynylene, propynylene, butynylene, and the like, in which the preferred one is propynylene or butynylene.

Suitable "halogen" and "halogen" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "mono(or di or tri)halo(C_1-C_4)alkyl", etc. may include fluorine, chlorine, bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms "hydroxy(lower)alkyl", "pyrazolyl(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and the like, in which the preferred one is C_1-C_4 alkyl and the most preferred one is methyl or isopropyl.

Suitable "lower alkenyl" moiety in the term "(2-methoxymethylmorpholino)(lower)alkenyl" may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, methylvinyl ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be C_2-C_4 alkenyl.

Suitable "aryl" may include phenyl, naphthyl, and the like, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl or naphthyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the terms "(lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl", "(lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl", etc. may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like, in which the preferred one is C_1-C_4 alkoxy and

the most preferred one is methoxy.

Suitable "substituent" in the terms "aryl which may be substituted with suitable substituent(s)" for R^1 and "aryl or indolyl, each of which may be substituted with suitable substituent(s)" for R^2 may include lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, tert-pentyl, hexyl, etc.), lower alkylenedioxy (e.g., methylenedioxy, ethylenedioxy, propylenedioxy, etc.), lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, etc.), lower alkoxy(lower)alkoxy(lower)alkoxy (e.g., (2-methoxyethoxy)-methoxy, etc.), mono(or di or tri)halo(lower)alkyl (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1 or 2-fluoroethyl, 1 or 2-bromoethyl, 1 or 2-chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, etc.), halogen (e.g., chlorine, bromine, fluorine and iodine), hydroxy, hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, 1-hydroxy-1-methylethyl, etc.), cyano, lower alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, etc.), lower alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, etc.), di(lower alkyl)aminosulfonyl (e.g., dimethylaminosulfonyl, diethylaminosulfonyl, etc.), pyrrolidinyl (e.g., 2-pyrrolidinyl, 3-pyrrolidinyl, pyrrolidino, etc.), morpholinyl (e.g., 2-morpholinyl, 3-morpholinyl, morpholino which may be substituted with lower alkyl as mentioned above or lower alkoxy(lower)alkyl (e.g., methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 1-ethoxyethyl, 2-ethoxyethyl, etc.), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, etc.), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl, etc.), and the like.

Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g., phenoxy, naphthoxy, etc.), an acid residue or the like.

Suitable "acid residue" may be halogen (e.g., chlorine, bromine, iodine, etc.), sulfonyloxy (e.g., methanesulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Preferred embodiments of the object compound (I) are as follows:

Y is lower alkylene (more preferably C_1-C_4 alkylene, most preferably methylene);

R^1 is aryl (more preferably C_6-C_{10} aryl, most preferably phenyl) which may be substituted with 1 to 3 (more preferably 1 or 2, most preferably 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), mono(or di or tri)-halo(lower)alkyl (more preferably trihalo(lower)alkyl, most preferably trifluoromethyl), lower alkylthio (more preferably C_1-C_4 alkylthio, most preferably methylthio), lower alkylsulfonyl (more preferably C_1-C_4 alkylsulfonyl, most preferably methylsulfonyl), di(lower alkyl)aminosulfonyl (more preferably di(C_1-C_4 alkyl)aminosulfonyl, most preferably dimethylaminosulfonyl), pyrrolyl (more preferably 1-pyrrolyl) and pyridyl (more preferably 4-pyridyl)];

R^2 is aryl (more preferably C_6-C_{10} aryl, most preferably phenyl or naphthyl) or indolyl, each of which may be substituted with 1 to 3 (more preferably 1 or 2) substituent(s) [more preferably substituent selected from the group consisting of lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl or

isopropyl), mono(or di or tri)halo(lower)alkyl (more preferably mono(or di or tri)halo(C_1-C_4)alkyl, most preferably difluoromethyl or trifluoromethyl), halogen (more preferably chlorine or fluoride), lower alkylenedioxy (more preferably C_1-C_4 alkylenedioxy, most preferably methylenedioxy or ethylenedioxy), lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), lower alkoxy(lower)alkoxy(lower)alkoxy (more preferably C_1-C_4 alkoxy(C_1-C_4)alkoxy(C_1-C_4)alkoxy, most preferably (2-methoxyethoxy)methoxy), hydroxy, hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)alkyl, most preferably hydroxymethyl or 1-hydroxy-1-methylethyl), cyano, pyrrolidinyl (more preferably pyrrolidino) and morpholinyl (more preferably morpholino) which may be substituted with lower alkoxy(lower)alkyl (more preferably C_1-C_4 alkoxy(C_1-C_4)alkyl, most preferably methoxymethyl) or lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl)];

R^3 is hydrogen; and

R^4 is (3-pyridyl)methyl;

(3-pyridyl)ethyl (more preferably 2-(3-pyridyl)ethyl);

3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl (more preferably 3-(3-pyridyl)-2-propenyl);

3-(3-pyridyl)propynyl (more preferably 3-(3-pyridyl)-2-propynyl);

pyrazolylmethyl (more preferably (4-pyrazolyl)methyl or (5-pyrazolyl)methyl) which may be substituted with hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)-alkyl, most preferably 2-hydroxyethyl);

pyrazolyl(lower)alkyl (more preferably pyrazolyl-(C_1-C_4)alkyl, most preferably (4-pyrazolyl)methyl, (5-pyrazolyl)methyl or 3-(4-pyrazolyl)propyl) which is substituted with lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl), (lower)alkoxy(lower)-

alkylmorpholinyl(lower)alkyl (more preferably (C_1-C_4)-alkoxy(C_1-C_4)alkylmorpholinyl(C_1-C_4)alkyl, most preferably 2-(2-methoxymethylmorpholino)ethyl) or (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl (more preferably (C_1-C_4)alkoxy(C_1-C_4)-alkylmorpholinylcarbonyl(C_1-C_4)alkyl, most preferably (2-methoxymethylmorpholino)carbonylmethyl);

piperidylmethyl (more preferably (4-piperidyl)methyl);

piperidyl(lower)alkyl (more preferably piperidyl(C_1-C_4)-alkyl, most preferably piperidinomethyl or (4-piperidyl)methyl) which is substituted with lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl) or (lower)alkoxy(lower)alkyl (more preferably (C_1-C_4)alkoxy(C_1-C_4)alkyl, most preferably ethoxymethyl);

(2,6-dimethylmorpholino)(lower)alkyl (more preferably (2,6-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,6-dimethylmorpholino)ethyl);

(3,3-dimethylmorpholino)(lower)alkyl (more preferably (3,3-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,3-dimethylmorpholino)ethyl);

(cis-3,5-dimethylmorpholino)(lower)alkyl (more preferably (cis-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more preferably ((3S,5S)-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-ethyl);

(2-methoxymethylmorpholino)(lower)alkyl (more preferably (2-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 3-(2-methoxymethylmorpholino)propyl or 2-(2-methoxymethylmorpholino)ethyl);

(3-methoxymethylmorpholino)(lower)alkyl (more preferably (3-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3-methoxymethylmorpholino)ethyl);

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5-methylmorpholino)-(C_1-C_4)alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino)ethyl);

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino)ethyl);

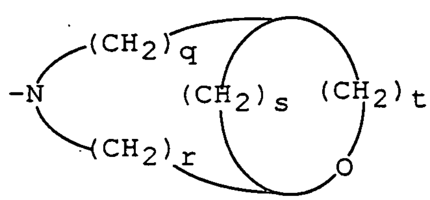
(3,5-dimethoxymethylmorpholino)(lower)alkyl (more preferably (3,5-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino)ethyl);

(2,3-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,3-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino)ethyl);

(2-methoxymethylmorpholino)(lower)alkenyl (more preferably (2-methoxymethylmorpholino)(C_2-C_4)alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl);

(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)alkyl (more preferably (5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(C_1-C_4)alkyl, most preferably 2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl); or

lower alkyl (more preferably C_1-C_4 alkyl, most preferably ethyl) which is substituted with a saturated heterocyclic group of the formula:



(wherein
r, s and t are each integer of 1 to 2, and
q is integer of 0 to 2)

(more preferably (1S,4S)-2-aza-5-oxabicyclo[2.2.1]-heptan-2-yl) which may be substituted with one or two lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl).

More preferred embodiments of the object compound (I) are as follows:

Y is lower alkylene (more preferably C_1-C_4 alkylene, most preferably methylene);

R^1 is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkoxy, mono(or di or tri)halo(lower)alkyl, lower alkylthio, lower alkylsulfonyl, di(lower alkyl)-aminosulfonyl, pyrrolyl and pyridyl [more preferably bis(trihalo(lower)alkyl)phenyl, (trihalo(lower)alkyl)((lower)alkoxy)phenyl, (trihalo(lower)alkyl)((lower)alkylthio)phenyl, (trihalo(lower)alkyl)((lower)alkylsulfonyl)phenyl, (trihalo(lower)alkyl)(di(lower alkyl)aminosulfonyl)-phenyl, (trihalo(lower)alkyl)(pyrrolyl)phenyl or (trihalo(lower)alkyl)(pyridyl)phenyl, most preferably 3,5-bis(trifluoromethyl)phenyl, 3-methoxy-5-trifluoromethylphenyl, 3-methylthio-5-trifluoromethylphenyl, 3-methylsulfonyl-5-trifluoromethylphenyl, 3-dimethylaminosulfonyl-5-trifluoromethylphenyl, 3-(1-pyrrolyl)-5-trifluoromethylphenyl or 3-(4-pyridyl)-5-trifluoromethylphenyl);

R^2 is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, hydroxy(lower)alkyl, cyano, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl [more preferably (lower)alkylenedioxy)phenyl, halophenyl, [trihalo(lower)alkyl]phenyl, (halo)((lower)alkyl)phenyl, (halo)[(lower)alkoxy]phenyl, (halo)(hydroxy)phenyl,

[trihalo(lower)alkyl](hydroxy)-phenyl, [hydroxy(lower)alkyl](hydroxy)phenyl, (cyano)(hydroxy)phenyl, (dihalo(lower)alkyl)(hydroxy)-phenyl, (lower alkyl)(hydroxy)phenyl, (lower alkyl)(pyrrolidinyl)phenyl, (lower alkyl)(morpholinyl)phenyl, (lower alkyl)[(lower)alkoxy-(lower)alkylmorpholinyl]phenyl or (lower alkyl)[(lower alkyl)morpholinyl]phenyl, most preferably 1,4-benzodioxan-6-yl, 4-fluorophenyl, 4-(trifluoromethyl)-phenyl, 4-fluoro-3-methylphenyl, 4-fluoro-3-methoxy-phenyl, 3-fluoro-4-methylphenyl, 4-chloro-3-hydroxy-phenyl, 3-hydroxy-4-(trifluoromethyl)phenyl, 3-hydroxy-4-(hydroxymethyl)phenyl, 3-hydroxy-4-methylphenyl, 3-hydroxy-4-(1-hydroxy-1-methylethyl)phenyl, 4-cyano-3-hydroxyphenyl, 3-hydroxy-4-(difluoromethyl)phenyl, 3-hydroxy-4-isopropylphenyl, 4-methyl-3-pyrrolidinophenyl or 4-methyl-3-morpholinophenyl] or indolyl;

R^3 is hydrogen; and

R^4 is (2,6-dimethylmorpholino)(lower)alkyl (more preferably (2,6-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,6-dimethylmorpholino)ethyl);

(3,3-dimethylmorpholino)(lower)alkyl (more preferably (3,3-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,3-dimethylmorpholino)ethyl);

(cis-3,5-dimethylmorpholino)(lower)alkyl (more preferably (cis-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more preferably ((3S,5S)-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-ethyl);

(2-methoxymethylmorpholino)(lower)alkyl (more preferably (2-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 3-(2-methoxymethylmorpholino)propyl or 2-(2-methoxymethylmorpholino)ethyl);

(3-methoxymethylmorpholino)(lower)alkyl (more preferably (3-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3-methoxymethylmorpholino)ethyl);
(2-methoxymethyl-5-methylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5-methylmorpholino)(C_1-C_4)-alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino)ethyl);
(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino)ethyl);
(3,5-dimethoxymethylmorpholino)(lower)alkyl (more preferably (3,5-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino)ethyl);
(2,3-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,3-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino)ethyl);
or (2-methoxymethylmorpholino)(lower)alkenyl (more preferably (2-methoxymethylmorpholino)(C_2-C_4)alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl).

The Processes 1 and 2 for preparing the object compound (I) of the present invention are explained in detail in the following.

<u>Process 1</u>

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (III) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde,

ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate (e.g. potassium carbonate, etc.), alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkyl-morpholine, N,N-di(lower)alkylethylamine (e.g. N,N-diisopropylethylamine, etc.), N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

<u>Process 2</u>

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to a reduction reaction.

The reaction can be carried out in the manner disclosed in Example 8 mentioned later or similar manners thereto.

The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-

mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, couph, expectoration, and the like;
ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;
cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;
pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like;
gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like;
inflammatory diseases such as nephritis, and the like;
circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the like;
epilepsy; spastic paralysis; pollakiuria; cystitis;
bladder detrusor hyperreflexia; urinary incontinence;
Parkinson diseases; dimentia; AIDS related dementia;
Alzheimer's diseases; Down's syndrome; Huntington's chorea;
carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by Helicobacter pylori or another spiral urease-positive gram-negative bacterium;
sunburn; angiogenesis or diseases caused by angiogenesis;
and the like.

It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic

obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; telalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis (e.g., nausea, retching, vomiting, acute emesis, delayed emesis, anticipatory emesis, past operative nausea and vomiting (PONV), acute and/or delayed emesis induced by drugs such as cancer chemotherapeutic agents, etc.); mental diseases, particularly anxiety, depression, dysthymic disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; and the like.

Furthermore, the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enternal,

intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention is shown in the following.

A. Evaluation of NK_1 antagonist transport efficiency to the central nervous system using a h-NK_1 receptor binding assay

[1] Test Method

(1) Administration of test compound and extraction of the compound from brain

Male SD rats were given an i.v. injection of a solution containing a test compound (1 mg/kg). 5 Min later the animals were anesthetized by ether, bled and perfused through

the aorta asscendens with 20 ml of saline. The brain was rapidly removed, weighed and homogenized in 4 vol. ice-cold distilled water by using Polytoron (KINEMATICA). To extract the test compound, 500 μl of the homogenate, 100 μl of methanol, 500 μl of 0.1 N NaOH and 4 ml of ethyl acetate were mixed by shaking for 10 min at room temperature. The organic phase (2.5 ml) was recovered by centrifugation at 3,000 rpm for 10 min, dried and dissolved in dimethyl sulfoxide.

(2) h-NK_1 receptor binding assay

(a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-NK_1 receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 5 μg/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 min), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in a buffer (25 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 5 μg/ml p-APMSF) and stored at -80° until use.

(b) ^{125}I-BH-Substance P binding to the prepared membrane

Cell membranes (6 μg/ml) were incubated with ^{125}I-BH-Substance P (0.1 nM) with or without the extracted compounds in 0.25 ml of a medium (50 mM Tris-HCl (ph 7.4), 5 mM $MnCl_2$, 20 μg/ml chymostatin, 40 μg/ml bacitracin, 4 μg/ml leupeptin, 5 μg/ml p-APMSF, 200 μg/ml BSA) at 22°C for 90 min. At the end of the incubation period, the contents were quickly filtered through a Blue Mat 11740 filter (pretreated with 0.1% polyethylenimine for 3 hours prior to use) by using

SKATRON Cell Harvester. The filter was then washed with a washing buffer (50 mM Tris-HCl (pH 7.4), 5 mM $MnCl_2$). The radioactivity was counted by using an auto gamma counter (Packard RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3 μM unlabeled Substance P.

[II] Test Result

All of the following Test Compounds showed more than 80% inhibition rate of ^{125}I-BH-Substance P binding to h-NK_1 receptors at the dose of 1 mg/kg.

Test Compounds: The object compounds of the Examples 4-(1), 4-(2), 7 and 8

B. Emesis in the dog

[I] Test Method

Individually housed adult female dogs (8 to 15 kg) were given an i.v. injection of a solution containing a test compound. 5 Min later the emetic responses (retching and vomiting) were induced by administration of subcutaneous apomorphine (0.1 mg/0.5 ml/kg) and observed for the next 60 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between experiments.

[II] Test Result

The following Test Compound showed 100% inhibition rate of emesis in the dog at the dose of 0.32 mg/kg.

Test compound: The object compound of the Example 4-(1)

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

(2-Methoxyethoxy)methyl chloride (4.87 ml) was added to a solution of 3-hydroxy-4-methylbenzoic acid (2.16 g) and N,N-diisopropylethylamine (9.2 ml) in 1,2-dichloroethane (40 ml) at room temperature. The mixture was stirred under reflux for 24 hours. After removal of the solvent by evaporation, the residue was partitioned between aqueous diluted hydrochloric acid solution and ethyl acetate. The organic layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude oil was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (3:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2-methoxyethoxy)methyl 3-[(2-methoxyethoxy)methoxy]-4-methylbenzoate (4.82 g) as an oil.

IR (Neat): 1725, 1595 cm^{-1}

NMR ($CDCl_3$, δ): 2.29 (3H, s), 3.37 (3H, s), 3.39 (3H, s), 3.54-3.90 (8H, m), 5.35 (2H, s), 5.60 (2H, s), 7.21 (1H, d, J=8.0Hz), 7.65 (1H, dd, J=1.6 and 8.0Hz), 7.74 (1H, d, J=1.4Hz)

MASS (API-ES): 351 $(M+Na)^+$

Preparation 2

Lithium aluminum hydride (0.35 g) was added by small portions over 12 minutes to an ice-cooled solution of (2-methoxyethoxy)methyl 3-[(2-methoxyethoxy)methoxy]-4-methylbenzoate (3.5 g) in tetrahydrofuran (20 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred at the same temperature for 30 minutes, 2N sodium hydroxide (0.5 ml) was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by

filtration and washed with tetrahydrofuran. The filtrate and the washing were combined, and evaporated under reduced pressure. The residue was dissolved into ethyl acetate, and manganese(IV) oxide (3.5 g) was added to the solution. After being stirred under reflux for 2 hours, the reaction mixture was filtered through Celite® and the insoluble mass was washed with ethyl acetate. The filtrate and the washing were combined and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 3-[(2-methoxyethoxy)methoxy]-4-methylbenzaldehyde (1.7 g) as an oil.

IR (Neat): 1687, 1407 cm^{-1}

NMR ($CDCl_3$, δ): 2.31 (3H, s), 3.38 (3H, s), 3.55-3.60 (2H, m), 3.82-3.87 (2H, m), 5.37 (2H, s), 7.30 (1H, d, J=7.7Hz), 7.44 (1H, dd, J=1.4 and 7.7Hz), 7.58 (1H, d, J=1.4Hz), 9.92 (1H, s)

MASS (API-ES): 279 $(M+Na+MeOH)^+$, 247 $(M+Na)^+$

Preparation 3

To a stirred mixture of 3-[(2-methoxyethoxy)methoxy]-4-methylbenzaldehyde (1.70 g) and 1,4-diacetyl-2,5-piperazinedione (1.6 g) in a mixture of N,N-dimethylformamide (17 ml) and tert-butanol (17 ml) was added potassium tert-butoxide (900 mg) at 5°C. The mixture was stirred for 24 hours at room temperature and then poured into water (300 ml). The aqueous mixture was adjusted to pH 4-5 with aqueous diluted hydrochloric acid solution and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using mixed solvents of toluene and ethyl acetate (3:1). The fractions containing the objective compound were

collected and evaporated under reduced pressure to give 1-acetyl-3-[3-[(2-methoxyethoxy)methoxy]-4-methylphenyl]-methylene-2,5-piperazinedione (2.05 g) as a powder.

IR (KBr): 3208, 1700, 1627, 1598, 1455, 1375 cm^{-1}

NMR ($CDCl_3$, δ): 2.26 (3H, s), 2.65 (3H, s), 3.27 (3H, s), 3.58-3.62 (2H, m), 3.81-3.86 (2H, m), 4.49 (2H, s), 5.32 (2H, s), 6.94 (1H, dd, J=1.5 and 7.8Hz), 7.15 (1H, d, J=7.8Hz), 7.23 (1H, d, J=1.5Hz), 7.27 (1H, s), 8.34 (1H, br s)

MASS (API-ES): 417 $(M+MeOH+Na)^+$

Preparation 4

A solution of 1-acetyl-3-[[3-[(2-methoxyethoxy)methoxy]-4-methylphenyl]methylene]-2,5-piperazinedione (2.0 g) in tetrahydrofuran (20 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 3 hours. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved into tetrahydrofuran (30 ml) and thereto was added hydrazine monohydride (1.5 ml). After being stirred for 1 hour at room temperature, the mixture was concentrated under reduced pressure. The residue was triturated with isopropyl alcohol and the resulting solid was collected by filtration to give 3-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-2,5-piperazinedione (1.75 g).

IR (KBr): 3183, 3060, 1675, 1454 cm^{-1}

NMR ($CDCl_3$, δ): 2.21 (3H, s), 2.95-4.00 (8H, m), 3.36 (3H, s), 4.20-4.27 (1H, m), 5.19 (1H, d, J=7.0Hz), 5.38 (1H, d, J=7.0Hz), 6.50 (1H, br s), 6.72 (1H, br s), 6.75 (1H, dd, J=1.4 and 7.9Hz), 6.97 (1H, d, J=1.4Hz), 7.08 (1H, d, J=7.9Hz)

MASS (APCI): 323 $(M+H)^+$, 247, 235

Preparation 5

Lithium aluminum hydride (0.62 mg) was added to an ice-cooled solution of 3-[3-[(2-methoxyethoxy)methoxy]-4-methyl]-benzyl-2,5-piperazinedione (1.7 g) in tetrahydrofuran (17 ml) below 5°C under nitrogen atmosphere. The mixture was stirred under reflux for 3.5 hours. After the mixture was cooled below 5°C, 2N sodium hydroxide was added to the mixture. After the mixture was stirred for 30 minutes at the same temperature, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure. The residue was dissolved into ethyl acetate, and the solution was dried over sodium sulfate and evaporated under reduced pressure to give 2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]piperazine (1.27 g) as an oil.

A solution of benzyloxycarbonyl chloride (0.75 g) in dichloromethane (1 ml) was added dropwise over 5 minutes to an ice-cooled solution of 2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.27 g) obtained by above procedure and triethylamine (2.2 ml) in dichloromethane (10 ml) below 5°C. After the mixture was stirred for 30 minutes at the same temperature, a solution of 3,5-bis(trifluoromethyl)-benzoyl chloride (0.93 ml) in dichloromethane (1.0 ml) was added dropwise to the mixture over 10 minutes below 5°C. After being stirred for 30 minutes at the same temperature, the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of toluene and ethyl acetate (5:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-4-(benzyloxycarbonyl)-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.61 g) as an oil.

IR (Neat): 2879, 1700, 1645 cm^{-1}

NMR ($CDCl_3$, δ): 2.19 (3H, s), 3.35 (3H, s), 2.40-5.40

(17H, m), 6.40-8.10 (10H, m), 7.82 (1H, br s)
MASS (APCI): 669 $(M+H)^+$

Preparation 6

A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-4-(benzyloxycarbonyl)-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (1.6 g) in methanol (20 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 4 hours. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.89 g) as an oil.

IR (Neat): 1732, 1714, 1705, 1647, 1431 cm^{-1}
NMR ($CDCl_3$, δ): 2.20 (3H, s), 2.50-5.20 (16H, m), 3.00 (3H, s), 6.40-7.40 (5H, m), 7.80 (1H, s)
MASS (API-ES): 557 $(M+Na)^+$, 535 $(M+H)^+$

Preparation 7

To a mixed solution of (3R)-3-(methoxymethyl)morpholine hydrochloride (4.71 g) and triethylamine (4.11 ml) in methanol (110 ml) was added 5.8M ethylene oxide (22 ml) in toluene solution at room temperature. After the reaction mixture was stirred at the same temperature for two days, it was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 2-[(3R)-3-methoxymethylmorpholino]ethanol (4.67 g) as an oil.

IR (Neat): 3433, 2860, 1454, 1119, 1055 cm^{-1}

NMR ($CDCl_3$, δ): 2.38-3.05 (5H, m), 3.33 (3H, s), 3.40-3.80 (8H, m)
MASS (APCI): 176 $(M+H)^+$

Preparation 8

The following compounds were obtained according to a similar manner to that of Preparation 8.

(1) 2-[cis-2,6-Dimethylmorpholino]ethanol
IR (Neat): 3431, 3402, 1456, 1373, 1325, 1146 cm^{-1}
NMR ($CDCl_3$, δ): 1.17 (6H, d, J=6.3Hz), 1.84 (2H, dd, J=10.2 and 11.4Hz), 2.52 (2H, t, J=5.5Hz), 2.71-2.78 (2H, m), 3.65 (2H, t, J=5.6Hz), 3.49-3.76 (2H, m)
MASS (APCI): 160 $(M+H)^+$

(2) 2-[(2S,5S)-2-Methoxymethyl-5-methylmorpholino]ethanol
IR (Neat): 3433, 3400, 1456, 1379, 1327, 1086, 1051 cm^{-1}
NMR ($CDCl_3$, δ): 1.19 (3H, d, J=6.3Hz), 1.88 (1H, d, J=10.8Hz), 1.96 (1H, t, J=10.5Hz), 2.54 (2H, t, J=5.5Hz), 2.72-2.83 (2H, m), 3.38 (3H, s), 3.36-3.45 (2H, m), 3.63 (2H, t, J=5.2Hz), 3.60-3.90 (2H, m)
MASS (APCI): 190 $(M+H)^+$

(3) 2-[(2S)-2-(Methoxymethyl)morpholino]ethanol
IR (Neat): 3435, 1456, 1354, 1302 cm^{-1}
NMR ($CDCl_3$, δ): 2.06 (1H, t, J=10.7Hz), 2.27 (1H, td, J=10.7 and 3.3Hz), 2.53-2.58 (2H, m), 2.68-2.84 (2H, m), 3.38 (3H, s), 3.38-3.44 (2H, m), 3.61-3.75 (4H, m), 3.89-3.98 (1H, m)
MASS (API-ES): 176 $(M+H)^+$, 198 $(M+Na)^+$

Preparation 9

To an ice-cooled solution of 2-[(3R)-3-methoxymethylmorpholino]ethanol (505 mg) in toluene (2.5 ml) was added dropwise a solution of thionyl chloride (429 mg) in toluene (1.5 ml) below 5°C under nitrogen atmosphere. The mixture was stirred at 70°C for 1.5 hours. After the mixture was cooled at room temperature, ethyl acetate was added to the mixture, and resulting suspension was evaporated under reduced pressure. Diisopropyl ether was added to the residue, and after the mixture was stirred at room temperature for 15 minutes, the resulting precipitates were collected by filtration, washed with diisopropyl ether and dried at 40°C under reduced pressure to give (3R)-4-(2-chloroethyl)-3-(methoxymethyl)morpholine hydrochloride (620 mg) as a light yellowish powder.

mp: 162-163°C
IR (KBr): 2945, 1140, 1109, 1084 cm^{-1}
NMR ($DMSO-d_6$, δ): 3.31 (3H, s), 3.10-4.10 (13H, m)
MASS (APCI): 194 $(M+H)^+$ (free)

Preparation 10

The following compounds were obtained according to a similar manner to that of Preparation 9.

(1) cis-2,6-Dimethyl-4-(2-chloroethyl)morpholine hydrochloride
IR (KBr): 1513, 1458, 1394, 1336, 1143 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.12 (6H, d, J=6.3Hz), 2.60-2.80 (2H, m), 3.44-3.50 (4H, m), 3.95-4.10 (4H, m)
MASS (APCI): 178 $(M+H)^+$ (free)

(2) (2S,5S)-4-(2-Chloroethyl)-2-methoxymethyl-5-methylmorpholine hydrochloride
IR (KBr): 2613, 1456, 1390, 1124, 1082 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.13 (3H, d, J=6.3Hz), 2.50-3.00 (3H, m), 3.27 (3H, s), 3.34-3.51 (7H, m), 4.03-4.10

(4H, m)

MASS (APCI): 208 $(M+H)^+$ (free)

(3) (2S)-4-(2-Chloroethyl)-2-(methoxymethyl)morpholine hydrochloride

NMR (DMSO-d_6, δ): 3.00 (2H, m), 3.27 (3H, s), 3.47 (4H, m), 3.75-4.12 (7H, m), 11.91 (1H, m)

MASS (APCI): 194 $(M+H)^+$ (free)

Preparation 11

Sodium triacetoxyborohydride (36.7 g) was added portionwisely to a mixture of (2S)-2-amino-1-propanol (10.0 g) and benzaldehyde (13.53 ml) in a mixture of dichloromethane (140 ml) and acetic acid (8.38 ml) at 0°C and the whole was stirred at room temperature overnight. The mixture was washed successively with 2N sodium hydroxide and brine, and dried over sodium sulfate. The solution was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S)-2-benzylamino-1-propanol (15.96 g).

IR (KBr): 2843, 1496, 1454, 1377, 1340, 1065 cm^{-1}

NMR ($CDCl_3$, δ): 1.10 (3H, d, J=6.4Hz), 2.77-2.93 (1H, m), 3.28 (1H, dd, J=10.6 and 6.9Hz), 3.61 (1H, dd, J=10.6 and 4.0Hz), 3.75, 3.87 (2H, ABq, J=13Hz), 7.21-7.34 (5H, m)

MASS (API-ES): 166 $(M+H)^+$

Preparation 12

(s)-(+)-Methyl glycidyl ether (8.25 ml) was added dropwise to a solution of (2S)-2-benzylamino-1-propanol (7.6 g) in methanol (7.6 ml) at room temperature. After being stirred at 40-50° for 24 hours, the solution was concentrated

under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-1-propanol (10.4 g) as an oil.

IR (Neat): 3400, 2929, 1452, 1414, 1373, 1329 cm^{-1}

NMR ($CDCl_3$, δ): 0.96 (3H, d, J=6.7Hz), 2.50-2.60 (1H, m), 2.57 (1H, dd, J=13.4 and 6.2Hz), 2.67 (1H, dd, J=13.4 and 6.5Hz), 2.95-3.10 (1H, m), 3.21-3.52 (4H, m), 3.30 (3H, s), 3.49 (1H, d, J=13.6Hz), 3.71-3.75 (1H, m), 3.83 (1H, d, J=13.6Hz), 7.21-7.37 (5H, m)

MASS (APCI): 254 $(M+H)^+$

Preparation 13

Triphenylphosphine (10.09 g) was added to a solution of (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-1-propanol (8.86 g) in tetrachloromethane (4.06 ml) at room temperature. After being stirred at room temperature for 2 days, the solution was concentrated under reduced pressure. The residue was triturated with diisopropyl ether (200 ml) three times, and the soluble portions were separated by decantation and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S)-1-[N-benzyl-N-[(1S)-2-chloro-1-methylethyl]amino]-3-methoxy-2-propanol (4.90 g) as an oil.

IR (Neat): 3463, 1452, 1362 cm^{-1}

NMR ($CDCl_3$, δ): 1.43 (3H, d, J=6.6Hz), 2.53-2.82 (4H, m), 3.30-3.39 (2H, m), 3.36 (3H, s), 3.59 (1H, d, J=13.6Hz), 3.83 (1H, d, J=13.6Hz), 3.79-3.87 (1H,

m), 4.01-4.09 (1H, m), 7.21-7.33 (5H, m)

MASS (APCI): 272 $(M+H)^+$

Preparation 14

A solution of (2S)-1-[N-benzyl-N-[(1S)-2-chloro-1-methylethyl]amino]-3-methoxy-2-propanol (1.90 g) in N,N-dimethylformamide (10 ml) was added to an ice-cooled suspension of sodium hydride (0.45 g, 60% in mineral oil) in N,N-dimethylformamide (10 ml) at 0°C. After being stirred for 1 hour at the same temperature, the mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2S,5S)-4-benzyl-2-methoxymethyl-5-methylmorpholine (0.86 g) as an oil.

IR (Neat): 2875, 1452, 1362, 1325, 1130, 1082 cm^{-1}

NMR ($CDCl_3$, δ): 1.15 (3H, d, J=6.3Hz), 1.73-1.93 (2H, m), 2.68-2.77 (2H, m), 3.35 (3H, s), 3.49 (2H, s), 3.31-3.49 (2H, m), 3.68-3.81 (2H, m), 7.25-7.32 (5H, m)

MASS (APCI): 236 $(M+H)^+$

Preparation 15

A solution of (2S,5S)-4-benzyl-2-methoxymethyl-5-methylmorpholine (0.86 g) in a mixture of concentrated hydrochloric acid (0.31 ml) and methanol (8.6 ml) was hydrogenated over 10% palladium-carbon (50% wet, 0.2 g) at room temperature under atmospheric pressure for 3 hours. After removal of the catalyst by filtration through Celite®, the filtrate was concentrated under reduced pressure to give (2S,5S)-2-methoxymethyl-5-methylmorpholine hydrochloride (0.71 g) as an oil.

IR (Neat): 3433, 3402, 2939, 1597, 1456, 1392, 1331, 1107 cm^{-1}

NMR ($DMSO-d_6$, δ): 1.12 (3H, d, J=6.3Hz), 2.49-2.75 (2H, m), 3.13-3.19 (2H, m), 3.27 (3H, s), 3.38 (2H, d, J=4.8Hz), 3.80-4.00 (2H, m)

MASS (APCI): 146 $(M+H)^+$ (free)

Preparation 16

N-Acetyl-3-methoxy-4-methyl-DL-phenylalanine (7.28 g) was dissolved into a mixture of water (36.5 ml) and 1N sodium hydroxide solution (29 ml). Cobalt(II) chloride hexahydrate (36.5 mg) and acylase (Acylase Amano, 365 mg) were added to the solution and the mixture was stirred at 37°C for 15.5 hours with controlling the pH of the reaction mixture to 7.5 with 1N sodium hydroxide solution. The insoluble material was removed by filtration and the pH of the filtrate was made to 3 with 6N hydrochloric acid, extracted with ethyl acetate, washed with water, dried over sodium sulfate, and evaporated in vacuo to give crude N-acetyl-3-methoxy-4-methyl-D-phenylalanine (3.17 g). The crude product was again subjected to the acylase reaction (cobalt(II) chloride hexahydrate 15.2 mg, acylase 152 mg, 37°C, pH 7.5, 20 hours) to give pure N-acetyl-3-methoxy-4-methyl-D-phenylalanine (2.70 g) as a viscous oil.

$[\alpha]_D^{26.8}$: -36.16° (C=0.424, MeOH)

IR (Neat): 3350, 1740, 1725 cm^{-1}

NMR ($CDCl_3$, δ): 1.99 (3H, s), 2.17 (3H, s), 3.00-3.30 (2H, m), 3.78 (3H, s), 4.75-4.90 (1H, m), 6.00-7.10 (3H, m), 6.36 (2H, br s)

MASS (APCI): 252 $(M+H)^+$

Preparation 17

A mixture of N-acetyl-3-methoxy-4-methylphenyl-D-alanine (2.55 g) in a mixture of 6N hydrochloric acid (25.5 ml) and toluene (18 ml) was stirred under reflux for 4 hours. After

being cooled to room temperature, the aqueous layer was separated and the organic layer was washed with water (10 ml) twice. The aqueous layer and the washings were combined and evaporated under reduced pressure. The resulting crystals were collected by filtration and washed with ice-water to give 3-methoxy-4-methyl-D-phenylalanine hydrochloride (1.35 g) as colorless crystals. The filtrate was evaporated under reduced pressure to give crude 3-methoxy-4-methyl-D-phenylalanine hydrochloride (0.6 g).

mp: 207-211°C

$[\alpha]_D^{27.2}$: +20.2° (C=0.5, H_2O)

IR (KBr): 1735, 1610, 1508 cm^{-1}

NMR (D_2O, δ): 2.18 (3H, s), 3.17 (1H, dd, J=7.6 and 14.6Hz), 3.32 (1H, dd, J=6.0 and 14.6Hz), 3.85 (3H, s), 4.27 (1H, dd, J=6.0 and 7.0Hz), 6.85 (1H, d, J=7.3Hz), 6.91 (1H, s), 7.21 (1H, d, J=8.0Hz)

MASS (APCI): 210 $(M+H)^+$ (free)

Preparation 18

Thionyl chloride (0.7 ml) was added dropwise to a solution of 3-methoxy-4-methyl-D-phenylalanine hydrochloride (1.75 g) in methanol (8 ml) over 10 minutes at room temperature. The whole was stirred at 40-50°C for 2 hours and then an additional thionyl chloride (0.7 ml) was added to the mixture. The whole mixture was stirred for further 1 hour and evaporated under reduced pressure. The resulting solid was triturated with diisopropyl ether and collected by filtration to give colorless crystals of 3-methoxy-4-methyl-D-phenylalanine methyl ester hydrochloride (1.70 g).

mp: 196-197°C

$[\alpha]_D^{30}$: -4.60° (C=0.5, MeOH)

IR (Nujol): 3400, 1741, 1583, 1465, 1446, 1249 cm^{-1}

NMR (D_2O, δ): 2.19 (3H, s), 3.21 (1H, dd, J=7.4 and 14.5Hz), 3.32 (1H, dd, J=6.0 and 14.5Hz), 3.85 (6H, s), 4.43 (1H, dd, J=6.0 and 7.4Hz), 6.82 (1H, dd,

J=1.4 and 7.6Hz), 6.87 (1H, d, J=1.4Hz), 7.22 (1H, d, J=7.6Hz)

MASS (APCI): 224 $(M+H)^+$ (free), 207, 164

Preparation 19

Potassium carbonate (1.70 g) was added by small portions with ice-cooling to a mixture of 3-methoxy-4-methyl-D-phenylalanine methyl ester hydrochloride (1.60 g) in mixed solvents of dichloromethane (7 ml) and water (9 ml). Chloroacetyl chloride (0.66 ml) was added to the mixture below 5°C over 15 minutes and then the whole was stirred for 30 minutes. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give an oil of (2R)-2-[N-(chloroacetyl)-amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester.

IR (Neat): 3305, 1737, 1643, 1583 cm^{-1}

Preparation 20

Benzylamine (1.65 g) and potassium carbonate (1.28 g) were added successively to a solution of (2R)-2-[N-(chloroacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester (1.85 g) in N,N-dimethylformamide (15 ml) at 20°C. After being stirred at 35°C for 1.5 hours, the mixture was poured into a mixture of ice-water (20 ml) and dichloromethane (20 ml). After the mixture was adjusted to pH 9 with diluted aqueous hydrochloric acid under stirring, the organic layer was separated, washed with brine (20 ml), dried over magnesium sulfate and evaporated under reduced pressure to give an oil of (2R)-2-[N-(benzylaminoacetyl)-amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester. A solution of (2R)-2-[N-(benzylaminoacetyl)amino]-3-(3-methoxy-4-methylphenyl)propionic acid methyl ester obtained by above procedure and acetic acid (0.18 ml) in isopropyl alcohol (10 ml) was stirred for 12 hours under

reflux.

After the mixture was cooled to room temperature, isopropyl ether was added to the mixture. The resulting precipitates were collected by filtration and washed with isopropyl ether to give colorless crystals of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine-2,5-dione (1.45 g).

mp: 205-209°C

$[\alpha]_D^{30}$: +11.12° (C=0.4, DMF)

IR (KBr): 3237, 1677, 1656, 1465, 1446, 1442 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.08 (3H, s), 2.76 (1H, d, J=17.2Hz), 2.87 (1H, dd, J=4.8 and 13.4Hz), 3.11 (1H, dd, J=4.8 and 13.4Hz), 3.46 (1H, d, J=17.2Hz), 3.69 (3H, s), 4.25 (1H, d, J=14.6Hz), 4.20-4.30 (1H, m), 4.52 (1H, d, J=14.6Hz), 6.54 (1H, dd, J=1.4 and 7.4Hz), 6.69 (1H, d, J=1.4Hz), 6.87 (1H, d, J=7.4Hz), 7.04-7.11 (2H, m), 7.24-7.30 (3H, m), 8.33 (1H, d, J=2.2Hz)

MASS (APCI): 339 $(M+H)^+$

Preparation 21

Lithium aluminum hydride (0.378 g) was added to an ice-cooled suspension of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)-2,5-piperazinedione (1.35 g) in tetrahydrofuran (22 ml) below 5°C under nitrogen atmosphere. The mixture was stirred under reflux for 3 hours. After the mixture was cooled below 5°C, 2N sodium hydroxide was added to the mixture. After the mixture was stirred for 30 minutes, the insoluble materials were removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure to give (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine as an oil. A solution of 3,5-bis(trifluoromethyl)benzoyl chloride (0.80 ml) in dichloromethane (1 ml) was added dropwise over 5 minutes to an ice-cooled solution of (3R)-1-benzyl-3-(3-methoxy-4-methylphenyl)piperazine obtained by above procedure

and triethylamine (0.84 ml) in dichloromethane (10 ml) below 5°C. After being stirred for 30 minutes at the same temperature, the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-methoxy-4-methylbenzyl)piperazine (1.92 g) as an oil.

IR (Neat): 2950, 2850, 1640, 1590, 1515 cm^{-1}

NMR ($CDCl_3$, δ): 2.16 (3H, s), 2.00-5.20 (14H, m), 6.25-6.32 (1H, m), 6.70-6.90 (2H, m), 7.20-7.44 (7H, m), 7.80 (1H, br s)

MASS (APCI): 551 $(M+H)^+$, 573 $(M+Na)^+$

Preparation 22

A solution of boron tribromide in dichloromethane (1M solution, 3.7 ml) was added dropwise over 20 minutes to an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-methoxy-4-methylbenzyl)-piperazine (0.68 g) in dichloromethane (5 ml). After being stirred at the same temperature for 2 hours, followed by further stirring at room temperature for 12 hours, the mixture was poured into aqueous saturated sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (4:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)piperazine (0.56 g) as a red foam.

IR (Neat): 1630, 1430 cm^{-1}

NMR ($CDCl_3$, δ): 2.00-5.20 (14H, m), 5.61 (1H, br s),

6.20-6.25 (1H, m), 6.60-7.70 (2H, m), 7.20-7.60 (7H, m), 7.80-7.85 (1H, m)

MASS (API-ES): 519 $(M-H_2O+H)^+$, 537 $(M+H)^+$, 559 $(M+Na)^+$

Preparation 23

Sodium hydride (60% in mineral oil, 18 mg) was added by small portions to an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)piperazine (0.20 g) in N,N-dimethylformamide (2 ml) below 5°C under nitrogen atmosphere. After the mixture was stirred for 5 minutes, (2-methoxyethoxy)methyl chloride (0.064 ml) was added to the mixture. The whole was stirred at room temperature for 2.5 hours, and thereto water was added. The whole was extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of hexane and ethyl acetate (7:3). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.21 g) as an oil.

IR (Neat): 2950, 1645, 1435 cm^{-1}

NMR ($CDCl_3$, δ): 2.19 (3H, s), 3.34 (3H, s), 2.00-5.20 (17H, m), 6.60-7.40 (10H, m), 7.70-7.80 (1H, m)

MASS (API-ES): 625 $(M+H)^+$, 647 $(M+Na)^+$

Preparation 24

A mixture of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-piperazine (0.38 g) in methanol (6 ml) was hydrogenated over 20% palladium hydroxide-carbon (0.06 g) at room temperature under atmospheric pressure for 8 hours. After removal of the catalyst by filtration through Celite®, the filtrate was concentrated under reduced pressure. The residue was

purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.32 g) as an oil.

IR (KBr): 3000-2700, 1629, 1513, 1444 cm^{-1}

NMR ($CDCl_3$, δ): 2.20 (3H, s), 2.50-5.30 (16H, m), 3.36 (3H, s), 6.40-7.50 (5H, m), 7.80 (1H, s)

MASS (API-ES): 535 $(M+H)^+$, 557 $(M+Na)^+$

Example 1

To a solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (440 mg) in N,N-dimethylformamide (2.2 ml) were added (3R)-4-(2-chloroethyl)-3-(methoxymethyl)morpholine hydrochloride (289 mg), potassium carbonate (434 mg) and potassium iodide (149 mg) at room temperature. The whole was stirred at 73°C for 2 hours. After being cooled to room temperature, the mixture was poured into ice-water and the aqueous mixture was made alkaline with saturated aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (40:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]-4-[2-[(3R)-3-methoxymethyl-morpholino]ethyl]piperazine (450 mg) as a light yellowish oil.

IR (Neat): 2879, 1639, 1437, 1281, 1136, 1009 cm^{-1}

NMR ($CDCl_3$, δ): 2.20 (3H, s), 1.95-5.40 (34H, m), 6.40-8.10 (6H, m)

MASS (APCI): 692 $(M+H)^+$

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-[3-[(2-methoxyethoxy)-methoxy]-4-methylbenzyl]piperazine

IR (Neat): 1680, 1643, 1508, 1435 cm^{-1}

NMR ($CDCl_3$, δ): 1.17 (6H, d, J=6.3Hz), 1.78 (2H, t, J=10.8Hz), 2.20 (3H, br s), 2.20-5.30 (23H, m), 3.36 (3H, s), 6.42-8.02 (6H, m)

MASS (APCI): 676 $(M+H)^+$

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine

IR (Neat): 2933, 2881, 1643, 1439, 1281, 1086, 1012 cm^{-1}

NMR ($CDCl_3$, δ): 1.18 (3H, d, J=6.2Hz), 1.78-1.96 (2H, m), 2.20 (3H, br s), 2.20-5.30 (25H, m), 3.37 (3H, s), 3.36 (3H, s), 6.66-7.80 (6H, m)

MASS (API-ES): 706.3 $(M+H)^+$, 728.3 $(M+Na)^+$

Example 3

1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[2-[(3R)-3-(methoxymethyl)morpholino]ethyl]piperazine (430 mg) was dissolved in methanol (10 ml) at room temperature, and methanesulfonic acid (0.215 ml) was added to the solution. After being stirred at the same temperature for 18 hours, the reaction mixture was concentrated until one third of original volume under reduced pressure, and poured into iced water. The aqueous mixture was made alkaline with 15% aqueous sodium

hydroxide solution, and the resulting mixture was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using mixed solvents of dichloromethane and methanol (30:1). The fractions containing the objective compound were collected and evaporated under reduced pressure, and the residue was treated with 4N hydrogen chloride in ethyl acetate solution to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-methylbenzyl]-4-[2-[(3R)-3-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride (280 mg) as a colorless powder.

mp: 167-172°C

$[\alpha]_D^{28}$: -8.50° (C=0.20, MeOH)

IR (KBr): 3400, 1645, 1429, 1282, 1184, 1138 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.08 (3H, s), 2.60-5.10 (25H, m), 6.18-7.10 (3H, m), 7.36-8.22 (3H, m), 9.25 (1H, br)

MASS (APCI): 604 $(M+H)^+$ (free)

Example 4

The following compounds were obtained according to a similar manner to that of Example 3.

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

mp: 188-200°C

$[\alpha]_D^{29}$: +0.70° (C=0.25, MeOH)

IR (KBr): 3402, 1643, 1516, 1429 cm^{-1}

NMR ($DMSO-d_6$, δ): 1.15 (6H, d, J=6.0Hz), 2.08 (3H, br s), 2.00 -5.10 (19H, m), 6.19-8.21 (6H, m)

MASS (APCI): 588 $(M+H)^+$ (free)

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-

methylmorpholino]ethyl]piperazine dihydrochloride

mp: 214-218°C

$[\alpha]_D^{29}$: +0.80° (C=0.25, MeOH)

IR (KBr): 3433, 3398, 1645, 1516, 1429, 1371, 1281, 1182, 1140 cm^{-1}

NMR ($DMSO-d_6$, δ): 1.16 (3H, d, J=6.0Hz), 2.08 (3H, br s), 2.50-5.10 (21H, m), 3.27 (3H, s), 6.20-8.20 (6H, m), 9.00-9.20 (1H, m)

MASS (APCI): 618 $(M+H)^+$ (free)

(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzoy)-4-[3-(3-pyridyl)-2-propynyl]piperazine

NMR ($CDCl_3$, δ): 0.60-5.30 (14H, m), 5.77 (1H, br s), 6.20-8.90 (10H, m)

MASS (APCI): 562 $(M+H)^+$

Example 5

The following compounds were obtained according to a similar manner to that of Example 1 and then a similar manner to that of Example 3.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

mp: 207-210°C

$[\alpha]_D^{26.2}$: -6.40° (C=0.4, MeOH)

IR (KBr): 3300, 3000, 2700, 1644, 1428 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.18 (3H, s), 2.20-5.20 (22H, m), 6.10-8.20 (6H, m), 9.00-9.40 (1H, br s), 11.00-12.00 (2H, m)

MASS (APCI): 604 $(M+H)^+$ (free)

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine dihydrochloride

IR (KBr): 1645, 1516, 1458, 1425, 1369 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.08 (3H, br s), 3.28 (3H, br s), 2.40-5.10 (22H, m), 6.19-8.22 (6H, m)
MASS (APCI): 604 $(M+H)^+$ (free)

Example 6

A mixture of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]piperazine (0.4 g), 1-chloro-3-(3-pyridyl)-2-propyne hydrochloride (0.17 g), potassium carbonate (0.52 g) and a trace of potassium iodide in N,N-dimethylformamide (7 ml) was stirred for 4 hours at 80°C. After cooling, the solvent was removed by evaporation, and ethyl acetate and aqueous sodium hydrogen carbonate solution were added thereto. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate. The fractions containing the objective compound were collected and evaporated under reduced pressure to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-[(2-methoxyethoxy)methoxy]-4-methylbenzyl]-4-[3-(3-pyridyl)-2-propynyl]piperazine (0.44 g) as an oil.

NMR ($CDCl_3$, δ): 0.60-5.60 (23H, m), 6.30-8.90 (10H, m)
MASS (APCI): 650 $(M+H)^+$

Example 7

A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]-piperazine (0.11 g) in methanol (10 ml) was treated with 4N hydrogen chloride in ethyl acetate (1 ml) and the mixture was evaporated under reduced pressure. The residue was triturated with a mixture of dichloromethane and ethyl acetate and the resulting powder was collected by filtration to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine

dihydrochloride (0.07 g).

mp: 180-190°C

IR (KBr): 1693, 1676, 1645, 1549, 1531, 1516, 1460, 1456, 1427, 1392, 1367, 1317, 1281, 1217, 1188, 1066 cm^{-1}

NMR (DMSO-d_6, δ): 1.60-5.20 (14H, m), 6.10-9.00 (10H, m)

MASS (APCI): 562 $(M+H)^+$ (free)

Example 8

A solution of 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]-piperazine (0.16 g) in a mixed solvent of methanol (10 ml) and tetrahydrofuran (10 ml) was hydrogenated over 10% palladium-charcoal (20 mg) at room temperature for 1.5 hours. After removal of catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate as an eluent. The fractions containing the objective compound were collected and evaporated under reduced pressure and the resulting residue was treated with 4N hydrogen chloride in ethyl acetate to give 1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine dihydrochloride (0.17 g) as a colorless solid.

mp: 60-70°C

IR (KBr): 1707, 1693, 1676, 1645, 1628, 1558, 1550, 1541, 1516, 1466, 1456, 1427, 1387, 1365, 1329, 1319, 1281, 1182, 1136, 1039 cm^{-1}

NMR (DMSO-d_6, δ): 1.80-5.20 (18H, m), 6.00-9.00 (10H, m)

MASS (APCI): 566 $(M+H)^+$ (free)

Preparation 25

A solution of 3-methoxy-p-toluic acid (45.32 g) in tetrahydrofuran (280 ml) was added to a suspension of sodium borohydride (9.29 g) in tetrahydrofuran (45 ml) with ice bath

cooling under nitrogen atmosphere. After 10 minutes stirring, boron trifuluoride diethyl etherate (41.5 ml) was added to the mixture at 3 to 15°C and the whole was stirred at room temperature overnight. Water (210 ml) and diisopropyl ether (60 ml) were added to the mixture. The organic layer was separated and the aqueous layer was extracted with diisopropyl ether (100 ml). The combined organic layer was washed successively with 1N sodium hydroxide solution and brine, dried over sodium sulfate, and evaporated in vacuo to give 3-methoxy-4-methylbenzylalcohol (41.63 g) as an oil.

IR (Neat): 3330, 1615, 1590, 1510, 1465, 1418, 1255 cm^{-1}

NMR ($CDCl_3$, δ): 1.70 (1H, br s), 2.21 (3H, s), 3.84 (3H, s), 4.65 (2H, s), 6.80-7.16 (3H, m)

<u>Preparation 26</u>

A mixture of 3-methoxy-4-methylbenzylalcohol (41.61 g), conc. hydrochloric acid (125 ml) and toluene (83 ml) was stirred at 90°C for 1 hour. After cooling, ice-water (125 ml) and diisopropyl ether (80 ml) were added to the mixture, and the organic layer was separated, and the aqueous layer was extracted with diisopropyl ether (160 ml). The combined organic layer was washed with saturated sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo to give 3-methoxy-4-methylbenzyl chloride (46.35 g) as an oil.

IR (Neat): 1615, 1590, 1510, 1470, 1415, 1255 cm^{-1}

NMR ($CDCl_3$, δ): 2.21 (3H, s), 3.85 (3H, s), 4.57 (2H, s), 6.82-7.15 (3H, m)

<u>Preparation 27</u>

3-Methoxy-4-methylbenzyl chloride (46.35 g) and ethyl acetamidomalonate (71.16 g) were added successively into a solution of sodium ethoxide (24.34 g) in ethanol (230 ml). The mixture was stirred under reflux for 2 hours, poured into

ice-water (690 ml) and the pH of the mixture was adjusted to 7 with 6N hydrochloric acid. The resulting precipitates were collected by filtration, washed with aqueous ethanol (3:1, 100 ml) and dried to give crude 2-acetylamino-2-(3-methoxy-4-methylbenzyl)malonic acid diethyl ester (85.03 g). A suspension of the crude product (80.66 g) in heptane (400 ml) was stirred at 50°C for 1 hour and cooled to room temperature. The resulting precipitates were collected by filtration, washed with heptane, and dried to give pure product (74.57 g) as a colorless crystals.

mp: 123-125°C

IR (KBr): 3251, 1747, 1643, 1518, 1267, 1213, 1190, 1051 cm^{-1}

NMR ($CDCl_3$, δ): 1.30 (6H, t, J=7.1Hz), 2.03 (3H, s), 2.16 (3H, s), 3.61 (2H, s), 3.76 (3H, s), 4.28 (4H, q, J=7.1Hz), 6.44-7.06 (4H, m)

Preparation 28

A mixture of 2-acetylamino-2-(3-methoxy-4-methylbenzyl)-malonic acid diethyl ester (10.0 g), potassium hydroxide solution (1.88 g) in water (25 ml) and ethanol (25 ml) were stirred under reflux for 1 hour. Another potassium hydroxide solution (1.88 g) in water (10 ml) was added to the mixture and the whole was stirred under reflux for 2 hours. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. Water (50 ml) and ethyl acetate (50 ml) were added to the resulting aqueous solution. The aqueous layer was separated and was adjusted to pH 1.5 with 6N hydrochloric acid. The solution was extracted with ethyl acetate, washed with brine, dried over sodium sulfate and evaporated under reduced pressure to give N-acetyl-3-methoxy-4-methyl-DL-phenylalanine (7.58 g) as a viscous oil.

IR (Neat): 3350, 1740, 1725 cm^{-1}

NMR ($CDCl_3$, δ): 1.99 (3H, s), 2.17 (3H, s), 3.00-3.30 (2H, m), 3.78 (3H, s), 4.75-4.90 (1H, m), 6.00-7.10

(3H, m), 6.37 (2H, br s)

Preparation 29

The following compounds were obtained according to a similar manner to that of Preparation 27.

(1) 2-Acetylamino-2-(4-chloro-3-methoxybenzyl)malonic acid diethyl ester
mp: 122-123°C
IR (KBr): 3247, 2977, 1749, 1643, 1523, 1309, 1205 cm^{-1}
NMR ($CDCl_3$, δ): 1.30 (6H, t, J=7.1Hz), 2.03 (3H, s), 3.64 (2H, s), 3.83 (3H, s), 4.16-4.35 (4H, m), 6.53 (1H, dd, J=2.0 and 8.0Hz), 6.56 (1H, d, J=2.0Hz), 6.56 (1H, s), 7.23 (1H, d, J=8.0Hz)
MASS (APCI): 372 $(M+H)^+$, 330, 282

(2) 2-Acetylamino-2-(4-fluoro-3-methoxybenzyl)malonic acid diethyl ester
mp: 128-131°C
IR (KBr): 2981, 1747, 1641, 1520, 1269, 1211 cm^{-1}
NMR ($CDCl_3$, δ): 1.30 (6H, t, J=7.1Hz), 2.04 (3H, s), 3.62 (2H, s), 3.82 (3H, s), 4.27 (4H, q, J=7.1Hz), 6.48-7.09 (4H, m)
MASS (APCI): 356 $(M+H)^+$

(3) 2-Acetylamino-2-(3,4-difluorobenzyl)malonic acid diethyl ester
IR (Nujol): 3259, 1749, 1645, 1518, 1317, 1277, 1205, 1051, 1016 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.16 (6H, t, J=7.1Hz), 1.91 (3H, s), 3.42 (2H, s), 4.15 (4H, q, J=7.1Hz), 6.76-7.45 (3H, m), 8.19 (1H, s)
MASS (APCI): 344 $(M+H)^+$, 302

(4) 2-Acetylamino-2-[3-methoxy-4-(trifluoromethyl)benzyl]-

malonic acid diethyl ester

mp: 119-120°C

IR (KBr): 3500-3150, 2700-2300, 1637, 1631, 1461, 1348, 1238, 1172 cm^{-1}

NMR ($CDCl_3$, δ): 1.31 (6H, t, J=7.2Hz), 2.04 (3H, s), 3.70 (2H, s), 3.84 (3H, s), 4.21-4.36 (4H, m), 6.57-6.64 (2H, m), 7.44 (1H, d, J=8.2Hz)

MASS (APCI): 406 $(M+H)^+$, 316

(5) 2-Acetylamino-2-(4-fluoro-3-methylbenzyl)malonic acid diethyl ester

IR (Neat): 3250, 1740, 1640, 1510, 1460, 1370, 1270, 1210, 1185 cm^{-1}

NMR ($CDCl_3$, δ): 1.30 (6H, t, J=7.1Hz), 2.03 (3H, s), 2.22 (3H, s), 3.58 (2H, s), 4.27 (4H, q, J=7.1Hz), 6.53 (1H, s), 6.70-6.95 (3H, m)

MASS (APCI): 340 $(M+H)^+$

Preparation 30

The following compounds were obtained according to a similar manner to that of Preparation 28.

(1) N-Acetyl-4-chloro-3-methoxy-DL-phenylalanine

mp: 177-179°C

IR (KBr): 3351, 3200-2500, 1735, 1629, 1548 cm^{-1}

MASS (APCI): 272 $(M+H)^+$, 230

(2) N-Acetyl-4-fluoro-3-methoxy-DL-phenylalanine

mp: 150-152°C

IR (KBr): 3340, 2947, 1718, 1603, 1514, 1259, 1215 cm^{-1}

NMR (DMSO-d_6, δ): 1.79 (3H, s), 2.74-3.07 (2H, m), 3.81 (3H, s), 4.41 (1H, m), 6.77 (1H, m), 7.01-7.14 (2H, m), 8.17 (1H, d, J=8.1Hz), 12.68 (1H, br)

MASS (APCI): 256 $(M+H)^+$

(3) N-Acetyl-3,4-difluorophenyl-DL-alanine
IR (KBr): 3360, 1710, 1615, 1550, 1530 cm^{-1}
NMR ($DMSO_6$, δ): 1.78 (3H, s), 2.50-2.88 (2H, m), 4.35-4.47 (1H, m), 7.07-7.41 (3H, m), 8.19 (1H, d, J=8.2Hz)
MASS (APCI): 244 $(M+H)^+$, 202

(4) N-Acetyl-3-methoxy-4-trifluoromethyl-DL-phenylalanine
mp: 156-160°C
IR (KBr): 3326, 3200-2300, 1716, 1621, 1552, 1459 cm^{-1}
NMR (DMSO-d_6, δ): 1.80 (3H, s), 2.85-3.50 (2H, m), 3.87 (3H, s), 4.23-4.54 (1H, m), 6.94 (1H, d, J=8.0Hz), 7.13 (1H, s), 7.52 (1H, d, J=8.0Hz), 8.23 (1H, d, J=8.1Hz), 12.82 (1H, br s)
MASS (APCI): 306 $(M+H)^+$ (free)

(5) N-Acetyl-4-fluoro-3-methyl-DL-phenylalanine
IR (Neat): 3350, 1720, 1600, 1540, 1500, 1345 cm^{-1}
NMR (DMSO-d_6, δ): 1.78 (3H, s), 2.20 (3H, s), 2.71-3.03 (2H, m), 4.31-4.42 (1H, m), 6.97-8.19 (3H, m), 12.68 (1H, br s)
MASS (APCI): 240 $(M+H)^+$

(6) N-Acetyl-3-fluoro-4-methyl-DL-phenylalanine
IR (Neat): 3300, 1740, 1720, 1600, 1540 cm^{-1}

<u>Preparation 31</u>

The following compounds were obtained according to a similar manner to that of Preparation 16.

(1) N-Acetyl-4-chloro-3-methoxy-D-phenylalanine
mp: 116-117°C
$[\alpha]_D^{27}$: -36.6° (C=0.37, MeOH)
IR (KBr): 3500-3150, 2700-2300, 1733, 1623 cm^{-1}
MASS (APCI): 272 $(M+H)^+$, 230

(2) N-Acetyl-4-fluoro-3-methoxy-D-phenylalanine
IR (Neat): 3330, 2940, 1728, 1618, 1518, 1275, 1223 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.79 (3H, s), 2.70-3.10 (2H, m), 3.81 (3H, s), 4.40 (1H, m), 6.78 (1H, m), 7.01-7.14 (2H, m), 8.18 (1H, d, J=8.1Hz), 12.63 (1H, br)
MASS (APCI): 256 $(M+H)^+$

(3) N-Acetyl-3,4-difluoro-D-phenylalanine
IR (KBr): 3395, 1720, 1615, 1545, 1515 cm^{-1}

(4) N-Acetyl-3-methoxy-4-trifluoromethyl-D-phenylalanine
mp: 156-160°C
IR (KBr): 3326, 3200-2300, 1716, 1621, 1552, 1459 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.80 (3H, s), 2.85-3.50 (2H, m), 3.87 (3H, s), 4.23-4.54 (1H, m), 6.94 (1H, d, J=8.0Hz), 7.13 (1H, s), 7.52 (1H, d, J=8.0Hz), 8.23 (1H, d, J=8.1Hz), 12.82 (1H, br s)
MASS (APCI): 306 $(M+H)^+$ (free)

(5) N-Acetyl-4-fluoro-3-methyl-D-phenylalanine
$[\alpha]_D^{28}$: -34.60° (C=0.5, MeOH)
IR (Nujol): 3400, 1715, 1605, 1530, 1500, 1450, 1240, 1200, 1120 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.78 (3H, s), 2.20 (3H, s), 2.71-3.03 (2H, m), 4.31-4.42 (1H, m), 6.97-8.19 (3H, m), 12.68 (1H, br s)
MASS (APCI): 240 $(M+H)^+$

(6) N-Acetyl-3-fluoro-4-methyl-D-phenylalanine
$[\alpha]_D^{29}$: -46.10° (C=0.5, MeOH)
IR (Nujol): 3300, 1705, 1600, 1560 cm^{-1}

Preparation 32

The following compounds were obtained according to a similar manner to that of Preparation 17.

(1) 4-Chloro-3-methoxy-D-phenylalanine hydrochloride
mp: 218-222°C
$[\alpha]_D^{27}$: +3.17° (C=0.52, MeOH)
IR (KBr): 3500-3150, 2700-2300, 1739, 1589, 1488 cm^{-1}
NMR (D_2O, δ): 3.19 (1H, dd, J=7.5 and 14.5Hz), 3.33 (1H, dd, J=5.7 and 14.5Hz), 3.91 (3H, s), 4.28 (1H, dd, J=5.7 and 7.5Hz), 6.89 (1H, dd, J=1.8 and 8.1Hz), 7.03 (1H, d, J=1.8Hz), 7.42 (1H, d, J=8.1Hz)
MASS (APCI): 230 $(M+H)^+$

(2) 4-Fluoro-3-methoxy-D-phenylalanine hydrochloride
mp: 210-220°C (decomp.)
IR (KBr): 1738, 1606, 1520, 1487, 1462, 1417, 1274, 1223, 1209, 1157, 1128 cm^{-1}
NMR (DMSO-d_6, δ): 3.13 (2H, m), 3.83 (3H, s), 4.00-4.40 (1H, m), 6.70-6.90 (1H, m), 7.00-7.30 (2H, m)
MASS (APCI): 214 $(M+H)^+$ (free)

(3) 3-Methoxy-4-trifluoromethyl-D-phenylalanine hydrochloride
mp: 156-160°C
IR (KBr): 3326, 3200-2300, 1716, 1621, 1552, 1459 cm^{-1}
NMR (D_2O, δ): 3.19 (1H, dd, J=7.5 and 14.4Hz), 3.33 (1H, dd, J=5.7 and 14.4Hz), 3.86 (3H, s), 4.20-4.26 (1H, m), 6.97 (1H, d, J=8.0Hz), 7.07 (1H, s), 7.58 (1H, d, J=8.0Hz)
MASS (APCI): 264 $(M+H)^+$ (free)

(4) 4-Fluoro-3-methyl-D-phenylalanine hydrochloride
IR (Nujol): 1735, 1485, 1460, 1375, 1210 cm^{-1}
MASS (APCI): 198 $(M+H)^+$ (free)

(5) 3-Fluoro-4-methyl-D-phenylalanine hydrochloride
IR (Nujol): 1730, 1480, 1555, 1250, 1220, 1200 cm^{-1}

Preparation 33

The following compounds were obtained according to a similar manner to that of Preparation 18.

(1) 4-Chloro-3-methoxy-D-phenylalanine methyl ester hydrochloride

mp: 165-168°C

IR (KBr): 3200-2500, 1745, 1583, 1494 cm^{-1}

NMR (D_2O, δ): 3.22 (1H, dd, J=7.5 and 14.5Hz), 3.35 (1H, dd, J=6.8 and 14.5Hz), 3.85 (3H, s), 3.92 (3H, s), 4.44 (1H, dd, J=6.8 and 7.5Hz), 6.89 (1H, dd, J=1.9 and 8.1Hz), 7.02 (1H, d, J=1.9Hz), 7.44 (1H, d, J=8.1Hz)

MASS (APCI): 244 $(M+H)^+$

(2) 4-Fluoro-3-methoxy-D-phenylalanine methyl ester hydrochloride

mp: 172-173°C

IR (KBr): 1745, 1610, 1581, 1518, 1452, 1398, 1294, 1273, 1242, 1215, 1163, 1120, 1061, 1028 cm^{-1}

NMR (DMSO-d_6, δ): 3.13 (2H, d, J=6.3Hz), 3.71 (3H, s), 3.83 (3H, s), 4.31 (1H, t, J=6.3Hz), 6.70-6.90 (1H, m), 7.00-7.30 (2H, m)

MASS (APCI): 228 $(M+H)^+$ (free)

(3) 3-Methoxy-4-trifluoromethyl-D-phenylalanine methyl ester hydrochloride

mp: 158-165°C

IR (KBr): 3326, 3200-2300, 1739, 1617, 1504, 1328 cm^{-1}

NMR (D_2O, δ): 3.29 (1H, dd, J=7.5 and 14.4Hz), 3.42 (1H, dd, J=5.7 and 14.4Hz), 3.85 (3H, s), 3.90 (3H, s), 4.46-4.55 (1H, m), 7.00 (1H, d, J=8.0Hz), 7.12 (1H, s), 7.65 (1H, d, J=8.0Hz)

MASS (APCI): 277 $(M+H)^+$ (free)

(4) 4-Fluoro-3-methyl-D-phenylalanine methyl ester hydrochloride

IR (Nujol): 3200, 1740, 1490, 1450, 1240 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.22 (3H, s), 3.00-3.17 (2H, m), 3.68 (3H, s), 4.21-4.28 (1H, m), 7.07-7.18 (3H, m), 8.67 (3H, s)

MASS (APCI): 212 $(M+H)^+$ (free)

(5) 3-Fluoro-4-methyl-D-phenylalanine methyl ester hydrochloride

IR (Nujol): 1740, 1580, 1510, 1450 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.21 (3H, s), 3.13 (2H, d, J=6.0Hz), 3.69 (3H, s), 4.29 (1H, t, J=6.0Hz), 6.95-7.28 (3H, m), 8.70 (3H, s)

MASS (APCI): 212 $(M+H)^+$ (free)

(6) 4-Fluoro-D-phenylalanine methyl ester hydrochloride

mp: 197.3-197.8°C

IR (KBr): 2989, 2956, 2910, 1745, 1741, 1504, 1490, 1450, 1240, 825 cm^{-1}

NMR ($DMSO-d_6$, δ): 3.10 (1H, dd, J=7.0 and 14.0Hz), 3.18 (1H, dd, J=6.4 and 14.0Hz), 3.67 (3H, s), 4.26 (1H, dd, J=6.4 and 7.0Hz), 7.11-7.33 (4H, m), 8.67 (3H, br s)

MASS: 198 $(M+H)^+$ (free)

(7) 4-Chloro-D-phenylalanine methyl ester hydrochloride

mp: 210-211°C

IR (KBr): 1743, 1707, 1693, 1645, 1547, 1541, 1514, 1495, 1454, 1240, 1186, 1147, 1126, 1099, 1061, 1024 cm^{-1}

NMR ($DMSO-d_6$, δ): 3.00-3.30 (2H, m), 3.68 (3H, s), 4.28 (1H, t, J=6.5Hz), 7.28 (2H, d, J=8.4Hz), 7.40 (2H, d, J=8.4Hz)

MASS (APCI): 214 $(M+H)^+$ (free)

(8) 4-Trifluoromethyl-D-phenylalanine methyl ester hydrochloride
mp: 198-199°C
IR (KBr): 3199, 2864, 1741 cm^{-1}
NMR ($DMSO-d_6$, δ): 3.10-3.30 (2H, m), 3.69 (3H, s), 4.35 (1H, t, J=6.4Hz), 7.51 (2H, d, J=8.1Hz), 7.71 (2H, d, J=8.1Hz)
MASS (APCI): 248 $(M+H)^+$ (free)

Preparation 34

The following compounds were obtained according to a similar manner to that of Preparation 19.

(1) (2R)-2-(2-Chloroacetylamino)-3-(4-chloro-3-methoxyphenyl)propionic acid methyl ester
mp: 68-69°C
IR (KBr): 3303, 2954, 1739, 1654, 1538 cm^{-1}
NMR ($CDCl_3$, δ): 3.13 (2H, d, J=6.0Hz), 3.75 (3H, s), 3.88 (3H, s), 4.05 (2H, s), 4.84-4.93 (1H, m), 6.65 (1H, dd, J=1.8 and 8.1Hz), 6.67 (1H, d, J=1.8Hz), 7.28 (1H, d, J=8.1Hz)
MASS (APCI): 320 $(M+H)^+$, 288, 260

(2) (2R)-2-(2-Chloroacetylamino)-3-(4-fluoro-3-methoxyphenyl)propionic acid methyl ester
mp: 86-87°C
IR (KBr): 1726, 1687, 1649, 1614, 1550, 1518, 1454, 1423, 1419, 1362, 1331, 1273, 1227, 1213, 1186 cm^{-1}
NMR ($CDCl_3$, δ): 3.12 (2H, d, J=5.8Hz), 3.75 (3H, s), 3.87 (3H, s), 4.05 (2H, s), 4.87 (1H, dt, J=8.0 and 5.8Hz), 6.40-7.20 (3H, m)
MASS (APCI): 304 $(M+H)^+$

(3) (2R)-2-(2-Chloroacetylamino)-3-(3,4-difluorophenyl)-propionic acid methyl ester

IR (Neat): 3305, 1470, 1675, 1660, 1515 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.87-3.11 (2H, m), 3.63 (2H, s), 4.03 (3H, s), 4.48-4.57 (1H, m), 7.03-7.41 (3H, m), 8.68 (1H, d, J=7.8Hz)

MASS (APCI): 292 $(M+H)^+$

(4) (2R)-2-(2-Chloroacetylamino)-3-[3-methoxy-4-(trifluoromethyl)phenyl]propionic acid methyl ester

mp: 108-109°C

IR (KBr): 3315, 2965, 1751, 1648, 1536, 1459, 1421 cm^{-1}

NMR ($CDCl_3$, δ): 3.10-3.29 (2H, m), 3.76 (3H, s), 3.89 (3H, s), 4.05 (2H, s), 4.87-4.97 (1H, m), 6.73-6.77 (2H, m), 7.00-7.05 (1H, m), 7.75 (1H, d, J=8.3Hz)

MASS (APCI): 354 $(M+H)^+$ 312

(5) (2R)-2-(2-Chloroacetylamino)-3-(4-fluoro-3-methylphenyl)propionic acid methyl ester

IR (Nujol): 3300, 1730, 1540, 1500, 1450 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.19 (3H, s), 2.82-3.06 (2H, m), 3.62 (3H, s), 4.06 (2H, s), 4.32-4.53 (1H, m), 6.97-7.13 (3H, m), 8.66 (1H, d, J=7.8Hz)

MASS (APCI): 288 $(M+H)^+$

(6) (2R)-2-(2-Chloroacetylamino)-3-(3-fluoro-4-methylphenyl)propionic acid methyl ester

IR (Nujol): 3300, 1740, 1660, 1540, 1450, 1360 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.19 (3H, s), 2.85-3.10 (2H, m), 3.63 (3H, s), 4.06 (2H, s), 4.45-4.56 (1H, m), 6.92-7.22 (3H, m), 8.68 (1H, d, J=7.8Hz)

MASS (APCI): 288 $(M+H)^+$

(7) (2R)-2-(2-Chloroacetylamino)-3-(4-fluorophenyl)-propionic acid methyl ester

IR (KBr): 3330, 1735, 1646, 1538, 1509, 1448, 1367, 1226, 1151 cm^{-1}

NMR ($CDCl_3$, δ): 3.09 (1H, dd, J=5.8 and 14.0Hz), 3.16 (1H, dd, J=5.8 and 14.0Hz), 3.74 (3H, s), 4.03 (2H, s), 4.85 (1H, ddd, J=5.8, 5.8 and 7.9Hz), 6.95-7.12 (5H, m)

MASS: 274 $(M+H)^+$

(8) (2R)-2-(2-Chloroacetylamino)-3-(4-chlorophenyl)-propionic acid methyl ester

mp: 87-88°C

IR (KBr): 1738, 1662, 1537, 1495, 1491, 1446, 1408, 1363, 1265, 1209, 1119, 1090, 1036, 1016 cm^{-1}

NMR ($CDCl_3$, δ): 2.90-3.30 (3H, m), 3.75 (3H, s), 4.03 (2H, s), 4.70-5.00 (1H, m), 7.05 (2H, d, J=8.0Hz), 7.28 (2H, d, J=8.0Hz)

MASS (APCI): 290 $(M+H)^+$

(9) (2R)-2-(2-Chloroacetylamino)-3-[4-(trifluoromethyl)-phenyl]propionic acid methyl ester

mp: 83-84°C

IR (KBr): 3294, 1741, 1655, 1547 cm^{-1}

NMR (DMSO-d_6, δ): 3.12-3.32 (2H, m), 3.76 (3H, s), 4.04 (2H, s), 4.86-4.96 (1H, m), 7.25 (2H, d, J=8.1Hz), 7.57 (2H, d, J=8.1Hz)

MASS (APCI): 324 $(M+H)^+$

Preparation 35

The following compounds were obtained according to a similar manner to that of Preparation 20.

(1) (3R)-1-Benzyl-3-(4-chloro-3-methoxybenzyl)piperazine-2,5-dione

mp: 149-150°C

$[\alpha]_D^{27}$: +6.38° (C=0.47, MeOH)

IR (KBr): 3253, 1658, 1461 cm^{-1}

NMR (DMSO-d_6, δ): 2.94 (1H, dd, J=4.7 and 13.4Hz), 2.96

(1H, d, J=17.4Hz), 3.14 (1H, dd, J=4.5 and 13.4Hz), 3.56 (1H, d, J=17.4Hz), 3.76 (3H, s), 4.21 (1H, d, J=14.6Hz), 4.30-4.35 (1H, m), 4.61 (1H, d, J=14.6Hz), 6.66 (1H, dd, J=1.8 and 8.0Hz), 6.91 (1H, d, J=1.8Hz), 7.04-7.11 (2H, m), 7.17 (1H, d, J=8.0Hz), 7.26-7.33 (3H, m), 8.38 (1H, br s)

MASS (APCI): 359 $(M+H)^+$

(2) (3R)-1-Benzyl-3-(4-fluoro-3-methoxybenzyl)piperazine-2,5-dione

mp: 177-179°C

IR (KBr): 3240, 1658, 1516, 1464 cm^{-1}

NMR ($CDCl_3$, δ): 3.00-3.30 (3H, m), 3.61 (1H, d, J=17.7Hz), 3.84 (3H, s), 4.20-4.60 (3H, m), 6.29 (1H, br s), 6.60-7.50 (8H, m)

MASS (APCI): 343 $(M+H)^+$

(3) (3R)-1-Benzyl-3-(3,4-difluorobenzyl)piperazine-2,5-dione

IR (KBr): 3313, 3255, 1650, 1515, 1465, 1275 cm^{-1}

NMR (DMSO-d_6, δ): 2.90-4.70 (7H, m), 6.94-7.32 (8H, m), 8.35 (1H, s)

MASS (APCI): 331 $(M+H)^+$

(4) (3R)-1-Benzyl-3-[3-methoxy-4-(trifluoromethyl)benzyl]-piperazine-2,5-dione

IR (KBr): 3315, 1751, 1648, 1536, 1459, 1421 cm^{-1}

NMR (DMSO-d_6, δ): 2.89-3.25 (2H, m), 3.19 (1H, d, J=17.5Hz), 3.62 (1H, d, J=17.5Hz), 3.77 (3H, s), 4.15 (1H, d, J=14.5Hz), 4.30-4.35 (1H, m), 4.68 (1H, d, J=14.5Hz), 6.80 (1H, d, J=8.0Hz), 7.00-7.41 (7H, m), 8.41 (1H, br s)

MASS (APCI): 393 $(M+H)^+$, 351

(5) (3R)-1-Benzyl-3-(4-fluoro-3-methylbenzyl)piperazine-2,5-

dione
$[\alpha]_D^{28}$: -15.60° (C=0.5, DMF)
IR (Nujol): 3250, 3225, 1650, 1430, 1320, 1250 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.13 (3H, s), 2.81-4.65 (7H, m), 6.83-7.34 (8H, m), 8.33 (1H, s)
MASS (APCI): 327 $(M+H)^+$

(6) (3R)-1-Benzyl-3-(3-fluoro-3-methylbenzyl)piperazine-2,5-dione
$[\alpha]_D^{27}$: -16.90° (C=0.5, DMF)
IR (Nujol): 3250, 1680, 1640, 1460, 1320 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.17 (3H, s), 2.84-4.69 (7H, m), 6.80-7.34 (8H, m), 8.35 (1H, s)
MASS (APCI): 327 $(M+H)^+$

(7) (2R)-2-[N-(Benzylaminoacetyl)amino]-3-(4-fluorophenyl)-propionic acid methyl ester
MASS: 345 $(M+H)^+$

(8) (3R)-1-Benzyl-3-(4-fluorobenzyl)piperazine-2,5-dione
mp: 190.1-190.8°C
IR (KBr): 1671, 1656, 1509, 1448, 1334, 1162 cm^{-1}
NMR ($CDCl_3$, δ): 3.08 (1H, d, J=4.4 and 14.0Hz), 3.19 (1H, d, J=5.9 and 14.0Hz), 3.05 (1H, d, J=17.7Hz), 3.56 (1H, d, J=17.7Hz), 4.33 (1H, m), 4.41 (1H, d, J=14.3Hz), 4.54 (1H, d, J=14.3Hz), 6.38-7.35 (10H, m)
MASS: 313 $(M+H)^+$

(9) (3R)-1-Benzyl-3-(4-chlorobenzyl)piperazine-2,5-dione
mp: 181-182°C
IR (KBr): 1678, 1649, 1564, 1550, 1516, 1489, 1462, 1433, 1408, 1325, 1273, 1178, 1112, 1090, 1063 cm^{-1}
NMR ($CDCl_3$, δ): 2.80-3.30 (3H, m), 3.57 (1H, d, J=17.6Hz), 4.20-4.40 (2H, m)), 4.60 (1H, d,

J=14.3Hz), 6.80-7.50 (9H, m)
MASS (APCI): 329 $(M+H)^+$

(10) (3R)-1-Benzyl-3-[4-(trifluoromethyl)benzyl]piperazine-2,5-dione
mp: 180-181°C
IR (KBr): 3257, 1678, 1651 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.86 (1H, d, J=17.3Hz), 3.00 (1H, dd, J=4.8 and 13.5Hz), 3.25 (1H, d, J=4.5 and 13.5Hz), 3.59 (1H, d, J=17.3Hz), 4.08 (1H, d, J=14.3Hz), 4.30-4.40 (1H, m), 4.73 (1H, d, J=14.3Hz), 7.05-7.32 (7H, m), 7.47 (2H, d, J=8.2Hz)
MASS (APCI): 363 $(M+H)^+$

Preparation 36

The following compounds were obtained according to a similar manner to that of Preparation 21.

(1) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine
IR (Neat): 1643, 1517 cm^{-1}
NMR ($CDCl_3$, δ): 2.00-5.20 (14H, m), 6.20-8.00 (11H, m)
MASS (APCI): 571 $(M+H)^+$

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-difluorobenzyl)-4-benzylpiperazine
IR (Neat): 1645, 1515, 1435, 1280, 1180, 1140 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.06-4.82 (11H, m), 6.61-8.19 (11H, m)
MASS (APCI): 543 $(M+H)^+$

Preparation 37

A solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine (2.23 g) and 1-chloroethyl chloroformate (0.61 ml) in 1,2-dichloroethane (10 ml) was stirred under reflux for 15 hours. After

cooling, the reaction mixture was concentrated under reduced pressure. The resulting syrup was dissolved into methanol (10 ml) and the solution was stirred under reflux for 2 hours. After cooling, the reaction mixture was concentrated under reduced pressure and the resulting powder was collected by filtration to give a yellow powder of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine hydrochloride (2.00 g).

mp: 70-71°C

MASS (APCI): 481 $(M+H)^+$

Preparation 38

A solution of boron tribromide in dichloromethane (1M solution, 6.0 ml) was added dropwise over 20 minutes to an ice-cooled solution of (2R)-1-[3,5-bis(trifluoromethyl)-penzoyl]-2-(4-chloro-3-methoxybenzyl)piperazine hydrochloride (0.98 g) in dichloromethane (5 ml). After being stirred at the same temperature for 2 hours, followed by at room temperature for 12 hours, an additional solution of boron tribromide in dichloromethane (1M solution, 4.0 ml) was added, and the whole was stirred at room temperature for further 4 hours. The resulting mixture was poured into aqueous saturated sodium hydrogen carbonate solution and the whole was stirred for 1 hour. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (20:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis-(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-piperazine (0.67 g) as a foam.

IR (Neat): 3400-3000, 1635 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.60-4.80 (10H, m), 6.28-7.20 (3H, m), 7.41 (1H, s), 7.75 (1H, s), 8.14 (1H, d, J=8.2Hz),

10.00 (1H, br s)
MASS (APCI): 467 $(M+H)^+$

Preparation 39

The following compounds were obtained according to a similar manner to that of Preparation 38.

(1) (2R)-4-Benzyl-2-(4-chloro-3-hydroxybenzyl)piperazine
mp: 65-68°C
IR (KBr): 2939, 2813, 1444, 1429, 1294, 1236, 1136, 1047 cm^{-1}
NMR ($DMSO-d_6$, δ): 1.60-4.00 (11H, m), 6.60 (1H, dd, J=1.6 and 8.0Hz), 6.78 (1H, d, J=1.6Hz), 7.16-7.40 (6H, m)

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-hydroxybenzyl)piperazine
mp: 82-86°C
IR (KBr): 3282, 1637, 1282, 1182, 1136 cm^{-1}
NMR ($CDCl_3$, δ): 2.20-5.20 (10H, m), 6.10-8.10 (6H, m)
MASS (APCI): 451 $(M+H)^+$

(3) (3R)-1-Benzyl-3-(3-hydroxy-4-methylbenzyl)piperazine
IR (KBr): 1649, 1516 cm^{-1}
NMR ($CDCl_3$, δ): 1.95-2.20 (2H, m), 2.20 (3H, s), 2.57-3.06 (7H, m), 3.51 (1H, d, J=13.1Hz), 3.52 (1H, d, J=13.1Hz), 6.60 (1H, d, J=7.4Hz), 6.61 (1H, s), 7.03 (1H, d, J=7.4Hz), 7.20-7.35 (5H, m)
MASS (APCI): 297 $(M+H)^+$

Preparation 40

To a solution of (2R)-2-(4-chloro-3-hydroxybenzyl)-4-benzylpiperazine (3.78 g) and triethylamine (5.71 ml) in dichloromethane was added 4-dimethylaminopyridine (0.29 g) and tert-butyldimethylsilyl chloride (5.30 g) successively

with ice bath cooling under nitrogen atmosphere. After stirring overnight at room temperature, water (50 ml) was added to the mixture and the organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with a mixture of dichloromethane and methanol (10:1) as eluent to give (2R)-4-benzyl-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]piperazine (4.11 g) as an oil.

IR (Neat): 1600, 1575, 1485, 1420, 1295, 1250, 1170, 1140 cm^{-1}

NMR ($CDCl_3$, δ): 0.15 (6H, s), 0.96 (9H, s), 1.80 (1H, t, J=10.0Hz), 1.94-2.98 (8H, m), 3.40 (1H, d, J=13.0Hz), 3.48 (1H, d, J=13.0Hz), 6.60-7.34 (8H, m)

MASS (APCI): 431 $(M+H)^+$, 397

Preparation 41

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.93 g) was added to a mixture of (2R)-4-benzyl-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]-piperazine (2.90 g) and 3-methoxy-5-(trifluoromethyl)benzoic acid (1.48 g), 1-hydroxybenzotriazole (1.14 g) in dichloromethane (18 ml) at room temperature.. After being stirred for 6 hours at the same temperature, the reaction mixture was poured into a mixed solvent of water (25 ml) and dichloromethane (15 ml). The aqueous layer was adjusted to pH 9 with aqueous sodium hydrogen carbonate solution. The organic layer was separated, washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (52 g) using a mixed solvent of hexane and ethyl acetate (2:1). The fractions containing the objective compound was collected and evaporated under reduced pressure to give a syrup of (2R)-1-[3-methoxy-5-(trifluoromethyl)-benzoyl]-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]-4-

benzylpiperazine (3.3 g).

IR (Neat): 2937, 1639, 1603, 1421, 1250, 1173, 1132, 847 cm^{-1}

NMR ($CDCl_3$, δ): 0.13 (6H, s), 1.00 (9H, s), 1.60-5.10 (11H, m), 3.81 (3H, s), 6.30-8.20 (11H, m)

MASS (APCI): 633 $(M)^+$

Preparation 42

The following compounds were obtained according to a similar manner to that of Preparation 37.

(1) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)piperazine

mp: 154-157°C

IR (KBr): 3265, 2956, 1624, 1427, 1173, 1128 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.20-4.90 (10H, m), 3.82 (3H, s), 6.20-7.30 (6H, m), 10.02 (1H, br)

MASS (APCI): 429 $(M+H)^+$

(2) (2R)-1-[3-Trifluoromethyl-5-(methylthio)benzoyl]-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]piperazine

IR (Neat): 1645, 1630, 1420, 1170, 1130 cm^{-1}

NMR ($CDCl_3$, δ): 0.18 (6H, s), 1.02 (9H, s), 2.48 (3H, s), 2.60-5.10 (10H, m), 6.28-8.26 (6H, m)

MASS (APCI): 559 $(M+H)^+$

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-fluoro-3-methoxybenzyl]piperazine hydrochloride

mp: 127-134°C

IR (KBr): 2970, 2947, 1645, 1520, 1281, 1184, 1136 cm^{-1}

NMR ($DMSO-d_6$, δ): 2.60-5.20 (12H, m), 6.50-8.30 (6H, m), 9.60 (2H, br)

MASS (APCI): 465 $(M+H)^+$ (free)

(4) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-[3-methoxy-5-

(trifluoromethyl)benzoyl]piperazine hydrochloride
IR (KBr): 1643, 1606, 1518, 1464, 1423, 1377, 1350, 1321, 1242, 1215, 1173, 1126, 1053, 1038 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.30-5.30 (16H, m), 6.30-7.50 (6H, m)
MASS (APCI): 427 $(M+H)^+$ (free)

(5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-difluorobenzyl)piperazine hydrochloride
IR (KBr): 3435, 2940, 2800, 1645, 1520, 1435, 1365, 1280, 1185, 1135 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.50-5.17 (9H, m), 6.60-8.45 (6H, m), 9.63 (2H, br s)
MASS (APCI): 453 $(M+H)^+$ (free)

(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine
IR (Neat): 2952, 1639, 1623, 1461, 1423, 1124 cm^{-1}
NMR ($CDCl_3$, δ): 2.60-5.20 (13H, m), 6.40-8.00 (6H, m)
MASS (APCI): 515 $(M+H)^+$

(7) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine
IR (Neat): 2950, 1637, 1461, 1423, 1317 cm^{-1}
NMR ($CDCl_3$, δ): 2.60-5.20 (15H, m), 6.60-7.60 (6H, m)
MASS (APCI): 477 $(M+H)^+$

(8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methylbenzyl)piperazine
IR (Neat): 3350, 1640, 1500, 1430, 1380, 1350, 1275 cm^{-1}
NMR ($DMSO-d_6$, δ): 2.00-4.84 (12H, m), 6.69-8.34 (7H, m)
MASS (APCI): 449 $(M+H)^+$

(9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-fluoro-4-methylbenzyl)piperazine
IR (Neat): 3300, 1625, 1425, 1275, 1120 cm^{-1}

NMR (DMSO-d_6, δ): 2.18 (3H, s), 2.40-4.86 (9H, m), 6.62-8.20 (6H, m)

MASS (APCI): 449 $(M+H)^+$

(10) (2R)-2-(4-Fluorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine hydrochloride

mp: 78.8-80.3°C

IR (KBr): 1513, 1423, 1349, 1172, 1126, 1054 cm^{-1}

NMR (DMSO-d_6, δ): 2.50-5.03 (9H, m), 3.82 (3H, s), 6.94-7.25 (8H, m), 9.56 (1H, br s)

MASS (APCI): 397 $(M+H)^+$ (free)

(11) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chlorobenzyl)piperazine hydrochloride

mp: 240-260°C

IR (Neat): 1658, 1496, 1437, 1387, 1362, 1331, 1282, 1186, 1132, 1101, 1059, 1018 cm^{-1}

NMR ($CDCl_3$, δ): 2.00-5.30 (9H, m), 6.70-8.50 (7H, m)

MASS (APCI): 451 $(M+H)^+$ (free)

(12) (2R)-2-(4-Chlorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine hydrochloride

IR (KBr): 1643, 1605, 1489, 1464, 1423, 1377, 1350, 1319, 1271, 1242, 1175, 1128, 1097, 1053 cm^{-1}

NMR (DMSO-d_6, δ): 2.00-5.40 (13H, m), 6.20-8.20 (7H, m)

MASS (APCI): 413 $(M+H)^+$ (free)

(13) (2R)-1-(3,5-Bis(trifluoromethyl)benzoyl)-2-[4-(trifluoromethyl)benzyl]piperazine

NMR ($CDCl_3$, δ): 2.30-5.30 (9H, m), 7.26-7.88 (7H, m)

MASS (APCI): 485 $(M+H)^+$

(14) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2951, 1632, 1608 cm^{-1}

NMR ($CDCl_3$, δ): 2.70-5.10 (9H, m), 3.80 (3H, s), 6.72-7.87 (7H, m)
MASS (APCI): 447 $(M+H)^+$

(15) (2R)-1-[3-Methoxy-5-(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)piperazine
$[\alpha]_D^{28.8}$: -46.15° (C=0.26, MeOH)
IR (Neat): 3740, 1630 cm^{-1}
NMR ($CDCl_3$, δ): 2.5-5.4 (9H, m), 3.55 (3H, s), 6.51 (1H, br s), 6.87 (1H, br s), 7.06 (1H, br s), 6.8-7.9 (7H, m)
MASS (APCI): 429 $(M+H)^+$

(16) (2R)-2-[(1H-Indol-3-yl)methyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine
IR (Neat): 3280, 1620, 1459, 1427 cm^{-1}
NMR ($CDCl_3$, δ): 2.60-3.00 (10H, m), 3.74 (3H, s), 6.70-7.40 (8H, m), 8.25-8.52 (1H, m)
MASS (APCI): 418 $(M+H)^+$

(17) (2R)-1-tert-Butoxycarbonyl-2-(3-hydroxy-4-methylbenzyl)piperazine
IR (KBr): 1674 cm^{-1}
NMR ($CDCl_3$, δ): 1.37 (9H, s), 2.20 (3H, s), 2.72-3.15 (8H, m), 3.90-3.93 (1H, m), 4.16 (1H, br s), 6.62 (1H, s), 6.68 (1H, d, J=7.6Hz), 7.02 (1H, d, J=7.6Hz)
MASS (APCI): 207 $(M+H-Boc)^+$

(18) (2R)-1-(tert-Butoxycarbonyl)-2-(4-chlorobenzyl)-piperazine
$[\alpha]_D^{27.2}$: +23.33° (C=0.39, MeOH)
IR (Neat): 3340, 2980, 2870, 2830, 1690, 1410, 1370 cm^{-1}
NMR ($CDCl_3$, δ): 1.36 (9H, s), 2.6-3.2 (7H, m), 3.90 (1H, br), 4.18 (1H, br s), 7.15 (2H, d, J=8.4Hz), 7.25

(2H, d, J=8.4Hz)
MASS (APCI): 311 $(M+H)^+$

Preparation 43

The following compounds were obtained according to a similar manner to that of Preparation 41.

(1) (2R)-1-[3-Trifluoromethyl-5-(methylthio)benzoyl]-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]-4-benzylpiperazine
IR (Neat): 1645, 1490, 1420, 1300, 1170, 1130 cm^{-1}
NMR ($CDCl_3$, δ): 0.15 (6H, s), 1.00 (9H, s), 1.95-5.02 (11H, m), 2.48 (3H, s), 6.20-8.25 (11H, m)
MASS (APCI): 649 $(M+H)^+$, 615

(2) (2R)-4-Benzyl-2-(4-fluoro-3-methoxybenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine
IR (Neat): 1738, 1643, 1628, 1616, 1604, 1516, 1464, 1454, 1417, 1371, 1342, 1273, 1099, 1055 cm^{-1}
NMR ($CDCl_3$, δ): 0.60-5.20 (17H, m), 6.00-7.50 (11H, m)
MASS (APCI): 517 $(M+H)^+$

(3) (2R)-4-Benzyl-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine
IR (Neat): 2811, 1643, 1280, 1180, 1137 cm^{-1}
NMR ($CDCl_3$, δ): 2.20-5.20 (17H, m), 6.40-7.50 (11H, m)
MASS (APCI): 567 $(M+H)^+$

(4) (2R)-4-Benzyl-2-(4-fluorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine
IR (Neat): 1639, 1509, 1460, 1423, 1344, 1128, 1010 cm^{-1}
NMR ($CDCl_3$, δ): 2.07 (1H, br), 2.73-4.91 (8H, m), 6.57-7.53 (12H, m)
MASS: 487 $(M+H)^+$

(5) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-chlorobenzyl)piperazine

IR (Neat): 1738, 1676, 1647, 1628, 1618, 1498, 1454, 1417, 1387, 1273, 1084, 1068 cm^{-1}

NMR ($CDCl_3$, δ): 0.60-5.20 (11H, m), 6.40-8.70 (12H, m)

MASS (APCI): 541 $(M+H)^+$

(6) (2R)-4-Benzyl-2-(4-chlorobenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

IR (Neat): 1707, 1678, 1643, 1630, 1618, 1604, 1516, 1496, 1489, 1477, 1454, 1417, 1392, 1375, 1342, 1317 cm^{-1}

NMR ($CDCl_3$, δ): 0.60-5.20 (14H, m), 6.40-8.20 (12H, m)

MASS (APCI): 503 $(M+H)^+$

(7) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2950, 2800, 1765, 1740, 1640 cm^{-1}

NMR (DMSO-d_6, δ): 1.70-4.30 (11H, m), 7.13 (1H, d, J=7.8Hz), 7.20-7.70 (10H, m), 8.13 (1H, d, J=7.8Hz)

MASS (APCI): 575 $(M+H)^+$

(8) (2R)-4-Benzyl-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2945, 2812, 1643 cm^{-1}

NMR ($CDCl_3$, δ): 2.04-5.10 (11H, m), 3.81 (3H, s), 6.73-7.93 (12H, m)

MASS (APCI): 537 $(M+H)^+$

(9) (2R)-4-Benzyl-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-2-(2-naphthylmethyl)piperazine

$[\alpha]_D^{28.8}$: -18.34° (C=0.35, MeOH)

IR (Neat): 3740, 1640 cm^{-1}

NMR ($CDCl_3$, δ): 1.9-2.4 (2H, m), 2.6-4.0 (11H, m), 4.4-5.2 (1H, m), 6.4-7.9 (15H, m)

MASS (APCI): 519 $(M+H)^+$

(10) (2R)-4-Benzyl-2-[(1H-indol-3-yl)methyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

IR (Neat): 3280, 1620, 1459 cm^{-1}

NMR ($CDCl_3$, δ): 2.00-5.20 (14H, m), 6.60-7.60 (13H, m), 7.90 (1H, br s)

MASS (APCI): 508 $(M+H)^+$

Preparation 44

To a solution of 4-fluoro-3-methoxybenzaldehyde (5 g) in methanol (25 ml) was added dropwise sodium borohydride (368 mg) in 0.1N sodium hydroxide aqueous solution (5 ml) in water bath and the whole was stirred for 1 hour. After the mixture was evaporated under reduced pressure, ethyl acetate and water were added thereto. The organic layer was separated and the water layer was further extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and concentrated in vacuo to give 4-fluoro-3-methoxybenzyl-alcohol (5.22 g) as an oil.

IR (Neat): 1610, 1516, 1462, 1417, 1315, 1277, 1149, 1115, 1032 cm^{-1}

NMR ($CDCl_3$, δ): 1.75 (1H, br s), 3.90 (3H, s), 4.64 (2H, s), 6.70-7.20 (3H, m)

Preparation 45

The following compounds were obtained according to a similar manner to that of Preparation 26.

(1) 4-Fluoro-3-methoxybenzyl chloride

IR (Neat): 1608, 1516, 1462, 1417, 1325, 1284, 1271, 1219, 1155, 1119, 1032 cm^{-1}

NMR ($CDCl_3$, δ): 3.91 (3H, s), 4.55 (2H, s), 6.70-7.20 (3H, m)

(2) 3-Methoxy-4-(trifluoromethyl)benzyl chloride

IR (Neat): 1606, 1459, 1272, 1174 cm^{-1}

NMR ($CDCl_3$, δ): 3.91 (3H, s), 4.73 (2H, s), 6.95 (1H, dd, J=0.6 and 8.0Hz), 7.04 (1H, d, J=0.6Hz), 7.53 (1H, d, J=8.0Hz)

Preparation 46

The following compound was obtained according to a similar manner to that of Preparation 24.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)piperazine

IR (Neat): 1641, 1633, 1626, 1514, 1475, 1462, 1452, 1446, 1435, 1423, 1417, 1385, 1340, 1336, 1273, 1095, 1063, 1045 cm^{-1}

NMR ($CDCl_3$, δ): 0.60-5.40 (12H, m), 6.20-8.60 (6H, m)

MASS (APCI): 465 $(M+H)^+$

Preparation 47

The following compound was obtained according to a similar manner to that of Preparation 17 followed by a similar manner to that of Preparation 18.

3,4-Difluorophenyl-D-alanine methyl ester hydrochloride

IR (KBr): 3400, 1735, 1610, 1235 cm^{-1}

NMR (DMSO-d_6, δ): 3.16 (2H, d, J=6.6Hz), 3.70 (3H, s), 4.33 (1H, t, J=6.6Hz), 7.05-7.52 (3H, m), 8.65 (3H, s)

MASS (APCI): 216 $(M+H)^+$ (free)

Preparation 48

28% Sodium methoxide in methanol (50 ml) was added to a solution of 3-fluoro-4-(trifluoromethyl)benzoic acid (20.8 g) in dimethylsulfoxide (200 ml). The mixture was stirred at 90°C for 3.5 hours. After cooling at room temperature, the

resulting mixture was poured into ice-water (1.5 l) and made acidic with diluted hydrochloric acid. After being stirred for 30 minutes, the resulting precipitates were collected by filtration and air-dried to give a colorless powder of 3-methoxy-4-(trifluoromethyl)benzoic acid (22.95 g).

mp: 203-204°C

IR (KBr): 3500-3150, 2700-2300, 1637, 1606, 1459, 1272, 1174 cm^{-1}

NMR ($DMSO-d_6$, δ): 3.95 (3H, s), 7.61-7.77 (3H, m), 13.45 (1H, s)

Preparation 49

Lithium aluminum hydride (4.53 g) was added by small portions to an ice-cooled solution of 3-methoxy-4-(trifluoromethyl)benzoic acid (23.3 g) in tetrahydrofuran (400 ml) under nitrogen atmosphere, and the mixture was stirred at room temperature for 2 hours. After being cooled with ice, 2N sodium hydroxide (2 ml) was added to the mixture under nitrogen atmosphere. The resulting precipitates were filtered off and washed with tetrahydrofuran, and the filtrate and washings were combined and evaporated under reduced pressure to give a crude oil. The oil was purified by column chromatography on silica gel using a mixture of dichloromethane and methanol (40:1) to give 3-methoxy-4-(trifluoromethyl)benzyl alcohol (20 g) as a colorless oil.

IR (Neat): 3500-3150, 2700-2300, 1637, 1606, 1459, 1272, 1174 cm^{-1}

NMR ($CDCl_3$, δ): 2.01 (1H, t, J=4.6Hz), 3.88 (3H, s), 4.72 (2H, d, J=4.6Hz), 6.95 (1H, dd, J=0.4 and 8.0Hz), 7.04 (1H, d, J=0.4Hz) 7.52 (1H, d, J=8.0Hz)

Preparation 50

A solution of 5-bromo-2-fluorotoluene (6 g) in ethyl ether (10 ml) and a catalytic amount of iodine were added to a suspension of magnesium (960 mg) in ethyl ether (10 ml)

under nitrogen atmosphere and the whole was refluxed for 30 minutes. After cooling, a solution of ethyl orthoformate (5.4 g) in ethyl ether (20 ml) was added to the mixture and the whole was stirred overnight. Sulfuric acid (10%, 20 ml) was added to the mixture and the organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with a mixture of hexane and ethyl acetate (10:1) as eluent to give 4-fluoro-3-methylbenzaldehyde as an oil.

IR (Neat): 1695, 1590, 1495, 1280, 1245, 1110 cm^{-1}

NMR ($CDCl_3$, δ): 2.36 (3H, s), 7.10-7.84 (3H, m), 9.93 (1H, s)

The obtained compound was dissolved in a mixture of methanol and tetrahydrofuran and sodium borohydride was added to the solution. After 1 hour of stirring, the solvent was removed and water was added to the residue. The mixture was made acidic with 10% sulfuric acid, extracted with ethyl acetate, washed with brine, dried over sodium sulfate, and evaporated in vacuo to give 4-fluoro-3-methylbenzylalcohol (1.33 g) as an oil.

IR (Neat): 3300, 1500, 1250 cm^{-1}

NMR ($CDCl_3$, δ): 2.28 (3H, s), 4.62 (2H, s), 6.93-7.26 (3H, m)

Preparation 51

Carbon tetrabromide (3.08 g) was added portionwisely to a solution of 4-fluoro-3-methylbenzylalcohol (1.3 g) and triphenylphosphine (2.9 g) in methylene chloride (50 ml) and the mixture was stirred for 1 hour. The solution was washed successively with saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was triturated with hexane and the resulting precipitate was removed by filtration. The filtrate was evaporated in vacuo and the residue was purified

by column chromatography on silica gel with hexane as eluent to give 4-fluoro-3-methylbenzylbromide (1.28 g) as an oil.

IR (Neat): 1500, 1250, 1200 cm^{-1}

NMR ($CDCl_3$, δ): 2.26 (3H, s), 4.45 (2H, s), 6.91-7.26 (3H, m)

Preparation 52

The following compound was obtained according to a similar manner to that of Preparation 50.

3-Fluoro-4-methylbenzylalcohol

IR (Neat): 3350, 1580, 1510, 1420, 1250 cm^{-1}

Preparation 53

The following compound was obtained by a similar manner to that of Preparation 51 followed by a similar manner to that of Preparation 27.

2-Acetylamino-2-(3-fluoro-4-methylbenzyl)malonic acid diethyl ester

IR (Nujol): 3250, 1740, 1630, 1510, 1360 cm^{-1}

NMR (DMSO-d_6, δ): 1.20 (6H, t, J=7.0Hz), 1.94 (3H, s), 2.19 (3H, s), 3.40 (2H, s), 4.10 (4H, q, J=7.0Hz), 6.67-7.23 (3H, m), 8.13 (1H, s)

MASS (APCI): 340 $(M+H)^+$

Preparation 54

The following compounds were obtained according to a similar manner to that of the first half of Preparation 21.

(1) (2R)-4-Benzyl-2-[4-chloro-3-methoxybenzyl]piperazine dihydrochloride

mp: 225-230°C (decomp.)

IR (KBr): 3398, 1460, 1419, 1246, 1030 cm^{-1}

NMR (DMSO-d_6, δ): 2.80-4.60 (11H, m), 3.87 (3H, s), 6.86

(1H, d, J=8.1Hz), 7.10 (1H, s), 7.30-7.60 (6H, m), 9.20-10.80 (3H, br)

MASS (APCI): 331 $(M+H)^+$ (free)

(2) (3R)-1-Benzyl-3-(4-fluoro-3-methoxybenzyl)piperazine

IR (Neat): 1666, 1608, 1516, 1456, 1419, 1321, 1275, 1217, 1151, 1126, 1034 cm^{-1}

NMR ($CDCl_3$, δ): 0.60-3.20 (9H, m), 3.58 (2H, s), 3.86 (3H, s), 6.50-7.10 (3H, m), 7.10-7.60 (5H, m)

MASS (APCI): 315 $(M+H)^+$

(3) (2R)-4-Benzyl-2-[3-methoxy-4-(trifluoromethyl)benzoyl]-piperazine

IR (Neat): 2938, 2809, 1614, 1583, 1506, 1459, 1421 cm^{-1}

NMR ($CDCl_3$, δ): 1.84-2.16 (2H, m), 2.50-3.01 (7H, m), 3.51 (2H, s), 3.88 (3H, s), 6.83-6.85 (2H, m), 7.25-7.33 (6H, m), 7.47 (1H, d, J=8.2Hz)

MASS (APCI): 365 $(M+H)^+$

(4) (2R)-4-Benzyl-2-(4-fluoro-3-methylbenzyl)piperazine

IR (Neat): 1500, 1450, 1320, 1245, 1205, 1120 cm^{-1}

NMR (DMSO-d_6, δ): 1.60-3.52 (14H, m), 6.95-7.40 (8H, m)

MASS (APCI): 299 $(M+H)^+$

(5) (2R)-4-Benzyl-2-(3-fluoro-4-methylbenzyl)piperazine

IR (Neat): 1575, 1510, 1450, 1320, 1250, 1130, 1110 cm^{-1}

(6) (2R)-4-Benzyl-2-(4-fluorobenzyl)piperazine

IR (Neat): 2937, 2807, 1508, 1450, 1326, 1135, 827, 742 cm^{-1}

NMR ($CDCl_3$, δ): 1.87 (1H, t, J=10.4Hz), 2.14 (1H, dt, J=3.8 and 11.0Hz), 2.35-2.94 (7H, m), 3.47 (1H, d, J=13.0Hz), 3.53 (1H, d, J=13.0Hz), 6.92-7.32 (9H, m)

MASS (APCI): 285 $(M+H)^+$

(7) (3R)-1-Benzyl-3-(4-chlorobenzyl)piperazine

IR (Neat): 1670, 1491, 1450, 1406, 1360, 1329, 1136, 1093, 1036, 1022 cm^{-1}

NMR ($CDCl_3$, δ): 1.70-3.80 (11H, m), 7.12 (2H, d, J=8.4Hz), 7.20-7.60 (7H, m)

MASS (APCI): 301 $(M+H)^+$

(8) (3R)-1-Benzyl-3-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 2939, 2810, 1676, 1618 cm^{-1}

NMR ($CDCl_3$, δ): 1.89 (1H, t, J=10.5Hz), 2.09 (1H, dt, J=3.9 and 11.0Hz), 2.55-3.04 (7H, m), 3.49 (1H, d, J=13.0Hz), 3.52 (1H, d, J=13.0Hz), 7.25-7.32 (7H, m), 7.55 (2H, d, J=8.1Hz)

MASS (APCI): 335 $(M+H)^+$

(9) (3R)-1-Benzyl-3-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride

mp: 212-225°C

IR (KBr): 3398, 2673, 1458, 1331 cm^{-1}

NMR (DMSO-d_6, δ): 3.00-4.50 (11H, m), 7.43-7.76 (9H, m)

MASS (APCI): 335 $(M+H)^+$ (free)

Preparation 55

The following compounds were obtained according to a similar manner to that of the latter half of Preparation 21.

(1) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)piperazine

IR (Neat): 1736, 1643, 1616, 1516, 1462, 1454, 1435, 1425, 1377, 1273, 1103, 1065, 1038 cm^{-1}

NMR ($CDCl_3$, δ): 0.60-5.20 (14H, m), 6.20-8.60 (11H, m)

MASS (APCI): 555 $(M+H)^+$

(2) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-methoxy-4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 1643, 1280, 1180, 1137 cm^{-1}
NMR ($CDCl_3$, δ): 2.20-5.20 (14H, m), 6.40-8.00 (11H, m)
MASS (APCI): 605 $(M+H)^+$

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methylbenzyl)-4-benzylpiperazine
IR (Neat): 1640, 1500, 1430, 1380, 1350, 1275, 1130 cm^{-1}
NMR (DMSO-d_6, δ): 2.00-4.83 (14H, m), 6.60-8.21 (11H, m)
MASS (APCI): 539 $(M+H)^+$

(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-fluoro-3-methylbenzyl)-4-benzylpiperazine
IR (Neat): 1640, 1430, 1280, 1170, 1130 cm^{-1}
NMR (DMSO-d_6, δ): 2.00-4.90 (11H, m), 2.16 (3H, s), 6.53-8.24 (11H, m)
MASS (APCI): 539 $(M+H)^+$

Example 9

The following compounds were obtained according to a similar manner to that of Example 1 using N,N-diisopropylethylamine instead of potassium carbonate as a base.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine dihydrochloride
mp: 160-169°C
$[\alpha]_D^{27}$: +10.0° (C=0.52, MeOH)
IR (KBr): 3500-3150, 2700-2300, 1644, 1423, 1282 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.00 (25H, m), 6.30-7.25 (3H, m), 7.43 (1H, s), 7.79 (1H, s), 8.17-8.22 (1H, m), 10.13 (1H, br s), 11.00-12.00 (2H, m)
MASS (APCI): 624 $(M+H)^+$ (free)

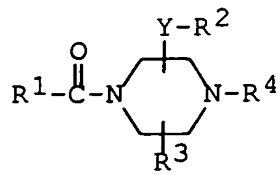
(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-

ethyl]piperazine dihydrochloride
mp: 180-190°C
$[\alpha]_D^{26.7}$: +13.90° (C=0.5, MeOH)
IR (KBr): 1676, 1645, 1547, 1516, 1464, 1427, 1392, 1387, 1367, 1321, 1282, 1217, 1184, 1136, 1034 cm^{-1}
NMR (DMSO-d_6, δ): 2.00-5.40 (28H, m), 6.30-8.30 (6H, m)
MASS (APCI): 622 $(M+H)^+$ (free)

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
mp: 146-159°C
$[\alpha]_D^{26.8}$: +10.67° (C=0.239, MeOH)
IR (KBr): 3435, 2656, 2598, 2467, 1647, 1429, 1329, 1282, 1180, 1132, 1068 cm^{-1}
NMR (DMSO-d_6, δ): 2.66-5.32 (27H, m), 7.10-8.30 (7H, m)
MASS (APCI): 642 $(M+H)^+$ (free)

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula :



wherein

Y is bond or lower alkylene,

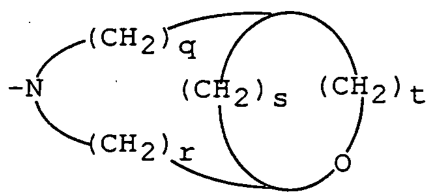
R^1 is aryl which may be substituted with suitable substituent(s),

R^2 is aryl or indolyl, each of which may be substituted with suitable substituent(s),

R^3 is hydrogen or lower alkyl, and

R^4 is (3-pyridyl)methyl;
(3-pyridyl)ethyl;
3-(3-pyridyl)propyl;
3-(3-pyridyl)propenyl;
3-(3-pyridyl)propynyl;
pyrazolylmethyl which may be substituted with hydroxy(lower)alkyl;
pyrazolyl(lower)alkyl which is substituted with lower alkyl,
(lower)alkoxy(lower)alkylmorpholinyl(lower)alkyl or
(lower)alkoxy(lower)alkylmorpholinylcarbonyl-(lower)alkyl;
piperidylmethyl;
piperidyl(lower)alkyl which is substituted with lower alkyl or
(lower)alkoxy(lower)alkyl;
(2,6-dimethylmorpholino)(lower)alkyl;
(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkyl;
(3-methoxymethylmorpholino)(lower)alkyl;
(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;
(2-methoxymethyl-5,5-dimethylmorpholino)(lower)-alkyl;
(3,5-dimethoxymethylmorpholino)(lower)alkyl;
(2,3-dimethoxymethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkenyl;
(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)-alkyl; or
lower alkyl which is substituted with a saturated heterocyclic group of the formula :



(wherein
r, s and t are each integer of 1 to 2, and
q is integer of 0 to 2)

which may be substituted with one or two lower alkyl,

and a salt thereof.

2. The compound of claim 1, in which
Y is lower alkylene;
R^1 is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkoxy, mono(or di or tri)halo(lower)alkyl, lower alkylthio, lower alkylsulfonl, di(lower alkyl)aminosulfonyl, pyrrolyl and pyridyl;
R^2 is phenyl which may be substituted with 1 or 2 substituent(s) selected from the group consisting

of lower alkyl, mono(or di or tri)halo(lower)alkyl, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, hydroxy(lower)alkyl, cyano, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl or indolyl;

R^3 is hydrogen; and

R^4 is 3-(3-pyridyl)propyl;

3-(3-pyridyl)propynyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkyl;

(3-methoxymethylmorpholino)(lower)alkyl;

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)-alkyl;

(3,5-dimethoxymethylmorpholino)(lower)alkyl;

(2,3-dimethoxymethylmorpholino)(lower)alkyl; or

(2-methoxymethylmorpholino)(lower)alkenyl.

3. A compound of claim 2, which is selected from the group consisting of

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-methylbenzyl]-4-[2-[(3R)-3-(methoxymethyl)morpholino]-ethyl]piperazine,

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine,

(4) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine,

(5) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

(7) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine,

(8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine,

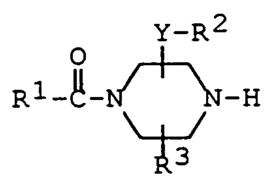
(9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine, and

(10) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine,

or a pharmaceutically acceptable salt thereof.

4. A process for the preparation of the compound of claim 1 or a salt thereof, which comprises,

(1) reacting a compound of the formula (II) :



(II)

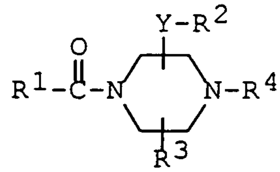
wherein R^1, R^2, R^3 and Y are each as defined in claim 1, or a salt thereof, with a compound of the formula (III) :

$$W_1\text{-}R^4 \qquad \text{(III)}$$

wherein R^4 is as defined in claim 1 and

W_1 is a leaving group,

or a salt thereof to give a compound of the formula (I) :

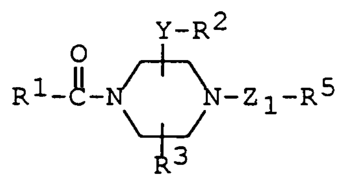


(I)

wherein R^1, R^2, R^3, R^4 and Y are each as defined in claim 1,

or a salt thereof, or

(2) subjecting a compound of the formula (Ia) :



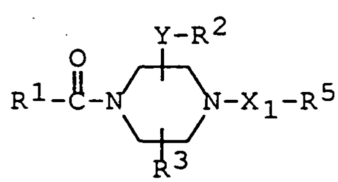
(Ia)

wherein R^1, R^2, R^3 and Y are each as defined above,

R^5 is 3-pyridyl, and

Z_1 is lower alkynylene,

or a salt thereof to a reduction reaction to give a compound of the formula (Ib) :



(Ib)

wherein R^1, R^2, R^3, Y and R^5 are each as defined above, and

X_1 is lower alkylene,

or a salt thereof.

5. A pharmaceutical composition which comprises, as an active ingredient, a compound of calim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

6. A compound of calim 1 for use as a medicament.

7. A method for treating or preventing Tachykinin-mediated diseases which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

8. A compound of claim 1 for use as Tachykinin antagonist.

9. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

DATED this 21st day of October

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Patent Attorneys for the Applicant